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A.S.P.E.N. Clinical Guidelines: Parenteral Nutrition Ordering, Order Review, Compounding, Labeling, and Dispensing

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Abstract

Background: Parenteral nutrition (PN) is a high-alert medication available for patient care within a complex clinical process. Beyond application of best practice recommendations to guide safe use and optimize clinical outcome, several issues are better addressed through evidence-based policies, procedures, and practices. This document provides evidence-based guidance for clinical practices involving PN prescribing, order review, and preparation. *Method*: A systematic review of the best available evidence was used by an expert work group to answer a series of questions about PN prescribing, order review, compounding, labeling, and dispensing. Concepts from the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) format were applied as appropriate. The specific clinical guideline recommendations were developed using consensus prior to review and approval by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. The following questions were addressed: (1) Does education of prescribers improve PN ordering? (2) What is the maximum safe osmolarity of PN admixtures intended for peripheral vein administration? (3) What are the appropriate calcium intake and calcium-phosphate ratios in PN for optimal neonatal bone mineralization? (4) What are the clinical advantages or disadvantages of commercially available premade ("premixed") multichambered PN formulations compared with traditional/customized PN formulations? (5) What are the clinical (infection, catheter occlusion) advantages or disadvantages of 2-in-1 compared with 3-in-1 PN admixtures? (6) What macronutrient dosing limits are expected to provide for the most stable 3-in-1 admixtures? (7) What are the most appropriate recommendations for optimizing calcium (gluconate) and (Na- or K-) phosphate compatibility in PN admixtures? (8) What micronutrient contamination is present in parenteral stock solutions currently used to compound PN admixtures? (9) Is it safe to use the PN admixture as a vehicle for non-nutrient medication delivery? (10) Should heparin be included in the PN admixture to reduce the risk of central vein thrombosis? (11) What methods of repackaging intravenous fat emulsion (IVFE) into smaller patient-specific volumes are safe? (12) What beyond-use date should be used for (a) IVFE dispensed for separate infusion in the original container and (b) repackaged IVFE? *(JPEN J Parenter Enteral Nutr.* XXXX;xx:xx-xx)

Keywords

parenteral formulas/compounding; nutrition; parenteral nutrition; nutrition; clinical guidelines; GRADE

Background

Parenteral nutrition (PN) is a vital therapeutic modality for neonates, children, and adults for a number of indications used in a variety of settings. Appropriate use of this complex therapy maximizes clinical benefit while minimizing the potential risk for adverse events. Complications occur both because of the PN admixture itself and the processes within which it is used. Many disparities exist in knowledge, skills, and PN practices, some of which can contribute to PN-related medication errors.[1] The 2004 revision of the Safe Practices for Parenteral Nutrition addressed the standardization of practices surrounding PN to improve care and to limit medication errors.[2] That publication remains a source document for A.S.P.E.N.'s ongoing commitment to patient safety with PN. The fact that PN is a high-alert medication requires healthcare organizations to

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develop evidence-based policies, procedures, and practices. Toward that end, A.S.P.E.N. is providing more current guidance documents for each healthcare organization to incorporate. The A.S.P.E.N. Clinical Guidelines work group, in partnership with the A.S.P.E.N. PN Safety Task Force, developed a number of questions related to PN practice that require adequate answers. While the task force developed PN Safety Consensus Recommendations[3] to address questions with limited evidence, the Clinical Guidelines work group took on the charge of evaluating the evidence for the remaining questions. The questions covering PN orders, order review, compounding, labeling, and dispensing are addressed in the current guidelines document.

Methodology

A.S.P.E.N. is an organization comprised of healthcare professionals representing the disciplines of medicine, nursing, pharmacy, dietetics, and nutrition science. The mission of A.S.P.E.N. is to improve patient care by advancing the science and practice of clinical nutrition and metabolism. A.S.P.E.N. vigorously works to support quality patient care, education, and research in the fields of nutrition and metabolic support in all healthcare settings. These Clinical Guidelines were developed under the guidance of the A.S.P.E.N. Board of Directors. Promotion of safe and effective patient care by nutrition support practitioners is a critical role of the A.S.P.E.N. organization. A.S.P.E.N. has been publishing Clinical Guidelines since 1986.[4-17]

These A.S.P.E.N. Clinical Guidelines are based upon general conclusions of health professionals who, in developing such Clinical Guidelines, have balanced potential benefits to be derived from a particular mode of medical therapy against certain risks inherent with such therapy. However, the professional judgment of the attending health professional is the primary component of quality medical care. Because guidelines cannot account for every variation in circumstances, the practitioner must always exercise professional judgment in the application of these guidelines. These Clinical Guidelines are intended to supplement, but not replace, professional training and judgment.

A.S.P.E.N. Clinical Guidelines have adopted concepts of the GRADE working group.[18-21] A full description of the methodology has been published.[22] Briefly, specific clinical questions where nutrition support is a relevant mode of therapy are developed and key clinical outcomes are identified. A rigorous search of the published literature is conducted, each included study is assessed for research quality, tables of findings are developed, and the body of evidence for the question is evaluated and graded. Randomized controlled clinical trials are initially graded as strong evidence but may be downgraded in quality based on study limitations. Controlled observational studies are initially graded as weak evidence but may be graded down further based on study limitations or upgraded based on study design strengths. In a consensus process, the authors make recommendations for clinical practice that are based on the evidence review assessed against consideration of the risks and benefits to patients. Recommendations are graded as strong when the evidence is strong and/or the risk vs benefit analysis is strong. Weak recommendations may be based on weaker evidence and/or weaker trade-offs to the patient. When limited research is available to answer a question, the recommendation is for further research to be conducted. The questions are summarized in Table 1.

Evaluating the safety of nutrition preparations and products often requires data derived from in vitro studies. Some of the vital safety-related questions with patient outcome implications that made use of in vitro evidence were included in this document. For example, in vitro data are necessary to evaluate stability, compatibility, and sterility. Although these studies do not align with the GRADE process, they are just as critical to the integrity of safe PN use in clinical practice. In these cases, the work group still conducted literature searches, evaluated the study quality, and provided evidence tables. Manuscripts were uniformly evaluated against quality criteria and are provided in the tables of evidence. The strength of recommendations based on in vitro data follows author considerations for potential risks to patients as well as the available evidence.

The Clinical Guideline authors, who represent a range of academic and clinical expertise, are involved in prescribing, reviewing, compounding, or labeling and dispensing PN. The external and internal expert reviewers, including the A.S.P.E.N. Board of Directors, have a similar, but even broader breadth of professional expertise. This Clinical Guideline is planned for revision in 2018.

Practice Guidelines and Recommendations

Question 1. Does education of prescribers improve PN ordering?

Recommendation: We suggest providing education to healthcare professionals to improve PN ordering, thereby reducing errors.

GRADE: Weak (Tables 2 and 3)

Rationale: PN is a complex prescription therapy associated with significant adverse effects. Deaths have occurred when safe practice guidelines were not followed.[2] Appropriate and safe prescribing/ordering of PN is a critical first step and an essential component of the PN-use process. The prescriber should be well versed in the appropriate indications for PN as well as vascular access devices (peripheral and central) and their associated complications. There are few known studies evaluating the impact of safe prescribing education programs on the outcomes of patients receiving PN. Interdisciplinary teams, applying education as part of an overall quality intervention, have been successful in reducing unnecessary PN use and decreasing errors.[23] In general medication prescribing,

Table 1. Summary: Clinical Guidelines Recommendations for Parenteral Nutrition Ordering, Order Review, Compounding, and Labeling/Dispensing.

Question	Recommendation	GRADE
1. Does education of prescribers improve PN ordering?	We suggest providing education to healthcare professionals to improve PN ordering, thereby reducing errors.	Weak
2. What is the maximum safe osmolarity of PN admixtures intended for peripheral vein administration?	We suggest that PN with an osmolarity up to 900 mOsm/L can be safely infused peripherally. Higher osmolarity limits, especially when peripheral PN is prepared as a TNA, may also be tolerated, but the evidence to support a safe limit is lacking.	Weak
3. What are the appropriate calcium intake and calcium-phosphate ratios in PN for optimal neonatal bone mineralization?	We recommend an elemental calcium intake of 76 mg/kg per day for short-term PN in neonates.	Strong
	We suggest a Ca:P ratio of 1.7:1 (mg:mg) or 1.3:1 (mmol:mmol) in short-term PN in neonates.	Weak
4. What are the clinical advantages or disadvantages of commercially available premade ("premixed") multichambered PN formulations compared with compounded PN formulations?	We suggest that commercially available premade multichambered PN formulations be considered as an available option for patients alongside compounded (customized or standardized) PN formulations to best meet an organization's patient needs.	Weak
5. What are the clinical (infection, catheter occlusion) advantages or disadvantages of 2-in-1 compared with 3-in-1 PN admixtures?	We suggest that there is no clinical difference in infectious complications between the two PN delivery systems. 3-in-1 formulations administered in the homecare setting may increase the risk for catheter occlusion and shorten catheter lifespan.	Weak
6. What macronutrient dosing limits are expected to provide for the most stable 3-in-1 admixtures?	We recommend that TNAs maintain final concentrations of amino acid ≥4%, monohydrated dextrose ≥10%, and injectable lipid emulsion ≥2% to be more likely to remain stable for up to 30 h at room temperature (25°C) or for 9 d refrigerated (5°C) followed by 24 h at room temperature.	Strong[a]
7. What are the most appropriate recommendations for optimizing calcium (gluconate) and (Na- or K-) phosphate compatibility in PN admixtures?	We cannot make a recommendation due to the multiple variations in amino acid concentrations, PN volume, pH, presence or absence of fat emulsion, or the amounts of other minerals (eg, magnesium). We suggest published graphs for specific products provide adequate guidance; however, no evidence indicates that these formulations remain stable for >24–48 h.	Weak[a]
8. What micronutrient contamination is present in parenteral stock solutions currently used to compound PN admixtures?	We suggest that, given the level of mineral contamination found in parenteral stock solutions used to compound PN admixtures, practitioners purchase products that accurately describe levels of contamination and also take that exposure into account when recommending or reviewing trace element dosing.	Weak
9. Is it safe to use the PN admixture as a vehicle for non-nutrient medication delivery?	We recommend that non-nutrient medication be included in PN admixtures *only* when supported by (1) pharmaceutical data describing physicochemical compatibility and stability of the additive medication and of the final preparation under conditions of typical use and (2) clinical data confirming the expected therapeutic actions of the medication; extrapolation beyond the parameter limits (eg, products, concentrations) of the given data is discouraged.	Strong[a]
10. Should heparin be included in the PN admixture to reduce the risk of central vein thrombosis?	We suggest that heparin not be included in PN admixtures for reducing the risk of central vein thrombosis.	Weak
11. What methods of repackaging IVFE into smaller patient-specific volumes are safe?	We recommend against the repackaging of IVFE into syringes for administration to patients. We suggest that other methodologies for repackaged IVFE, such as drawn-down IVFE units, are preferable.	Strong[a]
12. What beyond-use date should be used for (a) IVFE dispensed for separate infusion in the original container and (b) repackaged IVFE?	(a) We recommend that the BUD for unspiked IVFE in the original container should be based on the manufacturer's provided information. The BUD for IVFE in the original container spiked for infusion should be 12–24 h. (b) Although repackaged IVFE is not recommended, when used, the BUD for IVFE transferred from the original container to another container for infusion separately from a 2-in-1 PN solution should be 12 h.	Strong[a]

BUD, beyond-use date; Ca, calcium; IVFE, intravenous fat emulsions; P, phosphate; PN, parenteral nutrition; TNA, total nutrient admixture.
[a]Strength of recommendation makes use of evidence from in vitro studies.

Table 2. Evidence Summary, Question 1: Does Education of Prescribers Improve PN Ordering?

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Boitano, 2010[23]	OBS	Patients not described	To comply with A.S.P.E.N. ordering guidelines to reduce inappropriate PN ordering	Increased compliance with safe practice ordering after order form change and education (no *P* value)	Small sample size
Brown, 2007[28]	OBS	PN patients in NICU	To reduce PN prescribing error rate by implementing an ordering improvement process	Prescribing errors were decreased from 14.5% to 6.8% ($P = 0.016$)	Small sample size
Foulks, 1997[30]	OBS	Chart review of adult inpatients; 50 preintervention and 50 postintervention	To assist physicians in ordering PN specific to patient needs	A significant decrease in overfeeding of kilocalories 125% vs 110% ($P = 0.017$)	Small sample size
Mitchell, 1990[29]	OBS	PN patients on medical ward and intensive care unit	To aid in delivering standard nutrition care by using a new PN order form	Decrease in error rate (no *P* value)	Small sample size

NICU, neonatal intensive care unit; OBS, observational study; PN, parenteral nutrition.

Table 3. GRADE Table, Question 1: Does Education of Prescribers Improve PN Ordering?

Comparison	Outcome	Quantity, Type Evidence, Reference No.	Finding	GRADE	Overall Evidence GRADE
Preinteractive vs postinteractive computerized PN worksheet or form change	Prescribing errors	2 OBS[28,29]	Errors reduced	Low	Low
Pre- vs post- PN order form change	Overfeeding	2 OBS[23,30]	Overfeeding reduced	Low	
Pre- vs post- PN order form change	Pharmacy cost	1 OBS[23]	Cost reduced	Low	

OBS, observational study; PN, parenteral nutrition.

participating in education programs has been associated with safer practices.[24] Such programs are well received by students who perceive a large gap in their training in safe prescribing practices.[25-27] Specifically with PN prescribing, 4 small observational studies seem to show benefit in educating healthcare professionals.[23,28-30] Each of these studies had small sample sizes and implemented a new PN order form or system along with physician education as a primary or secondary goal. All 4 studies concluded that the new form and education led to a substantial decrease in overall PN prescription errors, overutilization of PN, overfeeding, and/or associated cost.[23,28-30]

Question 2. What is the maximum safe osmolarity of PN admixtures intended for peripheral vein administration?

Recommendation: We suggest that PN with an osmolarity of up to 900 mOsm/L can be safely infused peripherally. Higher osmolarity limits, especially when peripheral PN is prepared as a total nutrient admixture (TNA), may also be tolerated, but the evidence to support a safe limit is lacking.

GRADE: Weak (Tables 4 and 5)

Rationale: The administration of PN via a peripheral vein, often referred to as peripheral PN (PPN), is limited by tolerance to the concentrated macronutrient formula and high fluid volumes. The most significant complication limiting the tolerance of PPN is the development of thrombophlebitis. The incidence of thrombophlebitis is related to the osmotic content of the infused formula as well as the infusion rate. Osmolarity is a measure of the osmotically active particles in the solute (osmoles) per liter of solution. Dextrose and amino acids are significant contributors of solution osmolarity. Other factors that may influence the incidence of thrombophlebitis include addition of heparin,[31,32] addition of corticosteroid,[31] or the presence of fat emulsion when PPN is prepared as a TNA.[32-35] The coinfusion of intravenous fat emulsion (IVFE) has not been shown to reduce phlebitis.[36,37]

All available studies that have evaluated peripheral vein thrombophlebitis with infusion of PPN are limited by small sample size. Most are observational in study design. The osmolarity content of PPN regimens evaluated ranged from low

Table 4. Evidence Summary, Question 2: What Is the Maximum Safe Osmolarity of PN Admixtures Intended for Peripheral Administration?

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Williams, 1996[34]	OBS Prospective	Adult patients requiring PPN (n = 45) Formula 1: 650 mOsm/L (n = 23) Formula 2: 860 mOsm/L (n = 22) Provided as TNA, but content not specified.	Evaluate tolerance of TNA provided peripherally	No difference in phlebitis rate between formulas 36/45 tolerated for median of 8.5 d 7/45 developed phlebitis after median of 6 d (3/23 vs 4/22) 2/45 experienced extravasation	TNA formulas (up to 860 mOsm/L) well tolerated when infused peripherally.
Kane, 1996[35]	Randomized No control Not blinded	Adult patients requiring PPN (n = 39) Randomized to: "Standard": 1200 mOsm/L (n = 20) "High": 1700 mOsm/L (n = 19)	Evaluate tolerance of PN provided peripherally	No difference in phlebitis rate between formulas Standard group: 10/20 line failures (8 phlebitis, 2 occlusion); mean duration 6.8 d High group: 5/20 line failures (4 phlebitis, 1 occlusion); mean duration 6.3 d	TNA formulas (up to 1700 mOsm/L) well tolerated when infused peripherally Phlebitis rates of 20%–40% in 4–6 d Osmolarity rates >125 mOsm/h in all cases
Timmer, 1991[31]	OBS Prospective	Adult patients requiring PPN (n = 137) All PPN prepared as TNA Heparin 1000 units/L added to all bags Type 1: 829 mOsm/L (n = 34) Type 2: 842 mOsm/L (n = 30) Type 3: 860 mOsm/L (n = 30) Type 4: 790 mOsm/L (n = 32) Type 5: 1044 mOsm/L (n = 11) Administered via pump without filters	Evaluate tolerance of TNA provided peripherally and identify factors that induce phlebitis	The phlebitis rate at 48 h: Type 1 (4%), Type 2 (12%), Type 3 (24%), Type 4 (27%), Type 5 (91%) Phlebitis rate correlated with osmolarity rate, defined as mOsm/L × infusion rate (L/h)	TNA formulas (up to 790 mOsm/L) well tolerated when infused peripherally Tolerance best when osmolarity rate is limited to 84–99 mOsm/h
Hoheim, 1990[32]	OBS Prospective	Adult surgical patients requiring PPN (n = 23) PPN provided as TNA. Heparin 1000 units typically added Standard PPN formula contained 836 mOsm/L (base only) Fluid restricted PPN formula contained 964 mOsm/L (base only); 1200–1350 mOsm/L (including additives) Administered via pump without filters	Evaluate tolerance of TNA provided peripherally	PPN given for 2–12 d (average 5 d) 19/23 patients tolerated 4/23 patients experienced moderate to severe phlebitis 2/4 had no heparin added	TNA formulas (up to 1350 mOsm/L) well tolerated when infused peripherally Infusion rates titrated up slowly over several hours Addition of heparin may be a factor in enhancing vein tolerance IV sites were changed every 2.3 d on average
Bayer-Berger, 1989[37]	RCT Not blinded	Adult patients requiring PPN (n = 93) Randomized to: Group 1: 712 mOsm/kg; coinfusion of IVFE 10% (n = 27) Group 2: 803 mOsm/kg; coinfusion of IVFE 20% (n = 20) Group 3: 920 mOsm/kg; no IVFE (n = 21) Control group: maintenance solutions; 260–315 mOsm/kg (n = 25)	Compare the incidence of phlebitis in various PPN solutions with and without coinfusion of IVFE	Similar rates of phlebitis in group 1 (22%) and control (26%) at day 3 Higher phlebitis rate in groups 2 (48%) and 3 (44%) compared with control at day 3 with a resultant shorter duration of cannulation	PPN (712 mOsm/kg) + IVFE 10% is no more likely to cause phlebitis than maintenance solutions IVFE 20% did not provide a veno-protective effect

(continued)

Table 4. (continued)

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Daly, 1985[36]	Randomized No control Not blinded	Adult patients requiring PPN (n = 73) Randomized to: Group 1: 630 mOsm/L; no IVFE (n = 10) Group 2: 706 mOsm/L; coinfusion of IVFE (n = 14) Group 3: 882 mOsm/L; no IVFE (n = 23) Group 4: 983 mOsm/L; coinfusion of IVFE (n = 26) Using 0.45-µm inline filters	Assess the influence of IVFE when coinfused with PPN on incidence of phlebitis	No significant difference between groups in: • number of site changes per day or per patient • mean number of phlebitis events per day • average phlebitis score • incidence of infiltration	High osmolar solutions (up to 983 mOsm/L) tolerated as well as low osmolar solutions when infused peripherally Coinfusion of IVFE did not influence degree of phlebitis Measured osmolarity greater than calculated osmolarity
Gazitua, 1979[38]	OBS Prospective	Peripheral infusions (n = 83) • Solutions containing AA (525 ± 130 mOsm/L) (n = 67) • Solutions without AA (446 ± 101 mOsm/L) (n = 16) • Administered through a 0.22-µm filter	Assess the occurrence of phlebitis when AA solutions are infused peripherally	Overall phlebitis rate 54/83 (65%) AA solution: One phlebitis event per 48.9 h of infusion Non-AA solution: One phlebitis event per 88.6 h of infusion All solutions with osmolarity >600 mOsm/L produced phlebitis (n = 15) ($P < 0.01$) Phlebitis in 16/17 (94%) solutions with heparin vs 39/66 (59%) without heparin ($P < 0.05$)	Solutions were overall well tolerated peripherally Phlebitis in all solutions >600 mOsm/L No improvement when heparin added No IVFE provided
Isaacs, 1977[31]	OBS Prospective	Adult patients requiring IVF therapy (n = 15) Solutions alternated in random fashion. Rate = 125 mL/h without a pump or filters Group 1: 400 mOsm/L Group 2: 900 mOsm/L + heparin 500 units/L Group 3: 900 mOsm/L + heparin 500 units/L + cortisol 5 mg/L	Assess safety of infusing 900 mOsm/L peripherally without causing phlebitis	The interval between starting and stopping infusion was: Group 1: Infused 110 ± 40 h at same site Group 2: Infused 4 ± 3 h before stopping Group 3: Infused 120 ± 32 h before stopping	Infusion of 900 mOsm/L solution peripherally is feasible when heparin and cortisol added No IVFE provided

AA, amino acid; IVF, intravenous fluid; IVFE, intravenous fat emulsion; OBS, observational study; PN, parenteral nutrition; PPN, peripheral parenteral nutrition; RCT, randomized controlled trial; TNA, total nutrient admixture.

Table 5. GRADE Table, Question 2: What Is the Maximum Safe Osmolarity of PN Admixtures Intended for Peripheral Administration?

Comparison	Outcome	Quantity, Type Evidence, Reference No.	Finding	GRADE	Overall Evidence GRADE
Heparin vs no heparin	Phlebitis	2 OBS[31,38]	No difference	Low	Low
Low vs high osmolarity		3 OBS[32-34] 1 RCT[35]	TNA is well tolerated at osmolarity between 860 and 1700 mOsm/L; best at <100 mOsm/h	Low	
IVFE vs no IVFE		2 RCT[36,37]	No difference	Low	

IVFE, intravenous fat emulsion; OBS, observational study; RCT, randomized controlled trial; TNA, total nutrient admixture.

(400 mOsm/L) to high (1700 mOsm/L). The rate of infusion was often not controlled or described in the methods or in the results. Osmolarity rates <100 mOsm/h improve patient tolerance.[33] There is no consensus on what is considered a "tolerable" rate of thrombophlebitis or an acceptable duration of infusion before phlebitis occurs. Kane et al[35] accepted a thrombophlebitis rate of 30% and found that peripheral intravenous (IV) cannulas remained patent for an average of 6.3 days in patients receiving a high osmolarity (1700 mOsm/L) PPN. The high osmolarity PPN formula evaluated in this study contained IVFE prepared as a TNA. Older studies that did not incorporate IVFE with the PPN regimen or included the coinfusion of IVFE found that peripheral infusion was generally well tolerated with osmolarity limited to approximately 900 mOsm/L.[31,36-38]

Question 3. What are the appropriate calcium intake and calcium-phosphate ratios in PN for optimal neonatal bone mineralization?

Recommendation: We recommend an elemental calcium intake of 76 mg/kg per day for short-term PN in neonates.

GRADE: Strong (Tables 6 and 7)

Recommendation: We suggest a Ca:P ratio of 1.7:1 (mg:mg) or 1.3:1 (mmol:mmol) in short-term PN in neonates.

GRADE: Weak

Rationale: Although the body's pools of phosphorus and phosphate are in equilibrium, it is as phosphate that the mineral participates in biological processes and the form it takes in PN. This review initially attempted to study the ideal calcium-phosphate ratio (Ca:P) for the premature neonate on long-term PN therapy. Only studies of standard solutions using inorganic salts were included in the analysis. The longest study lasted 6 weeks, so true recommendations regarding long-term PN therapy cannot be made. In short-term PN, a Ca:P of 1.7:1 mg:mg (1.3:1 mmol:mmol) is associated with the best calcium and phosphate retention based on quantitative ultrasonography.[39] In short-term PN, a parenteral calcium intake of 75 mg/kg per day with a parenteral phosphate intake of 45 mg/kg per day may be associated with better bone strength.[39] The optimal methods to analyze calcium and phosphorus nutrition would be an analysis of bone mineral content and/or density. In short-term studies, calcium and phosphate retention rates serve as surrogates. In the face of recent product shortages, it is important to note that in a single study, provision of calcium and phosphate on alternate days in PN was associated with significant urinary losses of both calcium and phosphate on each day.[1]

Question 4. What are the clinical advantages or disadvantages of commercially available premade ("premixed") multichambered PN formulations compared with compounded PN formulations?

Recommendation: We suggest that commercially available premade multichambered PN products be considered as an available option for patients alongside compounded (customized or standardized) PN formulations to best meet an organization's patient needs.

GRADE: Weak (Tables 8 and 9)

Rationale: Commercially available PN formulations premade in single container or multichamber bags, often referred to as "premixed" although they require mixing in the pharmacy as part of their preparation, have been promoted as safer and more efficient delivery systems for macronutrients and micronutrients compared with traditional formulations prepared using manual or automated compounding techniques. Compounded PN formulations are often customized to a patient's needs (ie, custom) or may instead be prepared as institutionally defined specific standard formulations (ie, standard). However, the literature must be critically examined in order to determine the advantages and disadvantages of each delivery method. Most of the controlled clinical trials do not directly compare the use of "premixed" standard with compounded customized PN systems for patient outcomes, efficacy, or safety.[50-56] Rather, the available literature focuses on sequential evaluations of institutions after converting from one delivery approach to another system (ie, customized to standardized PN formulations). A majority of the literature is derived from European experiences, including some within the neonatal population. Primary outcome parameters have included labor and inventory costs, preparation time, nursing effort, and administration/delivery procedures. An A.S.P.E.N. Consensus Recommendation determined that the basis for identifying the best delivery system should be predicated upon the number and type of patients requiring PN within a specific healthcare organization.[57] The British Pharmaceutical Nutrition Group concluded that the appropriateness of the patient and the decision to use "premixed" PN formulations must be determined by appropriately trained nutrition support clinicians.[58] Three factors to be considered in making the final determination are the evaluation of clinical outcomes, safety, and cost.[59] Because of the limited availability of commercial products, many clinicians find that "premixed" PN formulations often will not meet the caloric, amino acid, and electrolyte needs of critically ill patients, who are often obese, require fluid restriction, and display hepatic/renal dysfunction. These products have particularly been criticized for their high dextrose concentrations, which could increase the risk of hyperglycemia and infection. Patient safety data are lacking for a reduction of errors associated with "premixed" PN products in relation to prescribing, compounding, and administration. Some studies do suggest cost and efficiency advantages in favor of commercially available "premixed" PN formulations over traditional modes of PN delivery. As a result, "premixed" PN formulations can be useful in appropriate patient populations when screened and assessed by suitably trained clinicians with expertise in nutrition support therapy.

Table 6. Evidence Summary, Question 3: What Are the Appropriate Calcium Intake and Calcium-Phosphate Ratios in PN for Optimal Neonatal Bone Mineralization?

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Pereira-da-Silva, 2011[39]	RCT PN with Ca 45 mg/kg per day (low dose) vs Ca 75 mg/kg per day (high dose). P at fixed Ca:P ratio (mg:mg) of 1.7:1	Neonates born ≤33 wk of gestational age, N = 86	Evaluate whether higher early Ca and P intake delivered by PN can prevent bone strength decline in preterm infants within the first weeks after birth	High-dose Ca significantly contributed to prevention of bone strength decline	High attrition rate; short-term study (6 wk)
Schanler, 1994[40]	Prospective OBS of mineral accretion on PN	LBW infants (<1.2 kg) needing PN for 3 wk, n for Ca = 12; n for P = 10	To determine nitrogen and mineral needs in parenterally nourished VLBW infants	Accretion of both Ca and P increased on PN; intakes predicted to achieve intrauterine accretion rates for Ca = 3.0 mmol/kg per day and P = 2.8 mmol/kg per day (Ca: 1 mmol = 40 mg; P: 1 mmol = 31 mg)	Small sample size; short-term study (3 wk); only studied mineral accretion
Prestridge, 1993[41]	RCT PN containing Ca:P at 1.25:1.5 mmol/dL vs 1.7:2.0 mmol/dL	LBW infants (<1.2 kg) needing PN for 3 wk, N = 24	To study mineral accretion and bone mineral content at various time points up to 26 wk	Apparent Ca retention (1.2 ± 0.2 vs 1.6± 0.2 mmol/kg per day) and P retention (1.4 ± 0.2 vs 1.8 ± 0.4 mmol/kg per day) differed significantly ($P < 0.01$) between standard and high groups, respectively. The absolute bone mineral content and the rate of increase in bone mineral content at all time points up to 26 wk were significantly greater in the high group than in the standard group.	The Ca:P (mg:mg) ratio in the standard group was 1.08:1 and in the high group was 1.1:1. The average duration of PN was just over 3 wk.
Pelegano, 1991[42]	RCT PN containing Ca:P of 1.3:1 vs 1.7:1 vs 2:1 mg:mg (these translate to Ca:P of 1:1, 1.3:1, 1.6:1 mol:mol)	Premature infants (<36 wk gestation) given PN for 48 h, N = 41	Evaluate the optimal Ca:P ratio in PN that is responsible for Ca and P retention	Ca retention was higher in the 2:1 and 1.7:1 groups and P retention was higher in the 1.3:1 and 1.7:1 groups. The 1.7:1 had the highest absolute retention of Ca and P.	Extremely short-term study (48 h); only studied mineral accretion
Aiken, 1989[43]	OBS Regimen 1 = Ca 9.5 mmol/L and P 7.3 mmol/L Regimen 2 = Ca 9.5 mmol/L and P 11.6 mmol/L Ca:P of 1.3:1 vs 0.8:1 mmol/L:mmol/L	Premature infants (28–35 wk gestation) given PN starting in the first week of life, N = 61	To evaluate mineral balance studies in sick preterm intravenously fed infants during the first week after birth	Phosphate deficiency developed in infants given regimen 1, who had higher urine Ca excretion, lower percentage Ca retention, and lower plasma phosphate levels than those given regimen 2. In infants given regimen 2, mean Ca retention from admission to day 7 was 3.9 mmol/kg and after day 10 was 0.9 mmol/kg per day.	Only able to obtain abstract to work with
Pelegano, 1989[44]	RCT PN with Ca 36 vs 76 mg/kg per day; Ca:P 1.7:1 (mg:mg)	Premature infants (<36 wk gestation) studied between days 3 and 8 of life, N = 25	To evaluate Ca and P balance at increasing amounts of Ca and P while maintaining a mg:mg ratio of Ca:P of 1.7:1 (1.3:1 mmol:mmol ratio)	The absolute amounts of Ca and P increased as increasing amounts of Ca and P were given. The percentage of Ca retained (89%–94%) and the percentage of P retained (86%–92%) varied little.	

(continued)

Table 6. (continued)

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Koo, 1989[45]	RCT PN with 5 mmol Ca and P vs 15 mmol Ca and P; standard vitamin D	Premature infants (<30 wk gestation but enrolled at 18–21 d of life) given PN for a median of 33 d, N = 26	To evaluate biochemical parameters and urinary excretion of Ca and P in neonates provided high and low Ca and P intakes	No difference in serial measurements of serum Ca, Mg, P, alkaline phosphatase, vitamin D, creatinine, and urinary Ca/creatinine ratios; 4 infants in the low Ca and P group developed hypophosphatemia and had consistently higher urinary tubular reabsorption ratios of P. Severe bone demineralization occurred in 2 infants in the low Ca and P group.	
Vileisis, 1987[46]	RCT PN with Ca intake was kept constant at 30 mg/kg per day with 3 different P intakes (low: 30 mg/kg per day, moderate: 40 mg/kg per day, and high: 50 mg/kg per day)	Premature infants (<1500 g given PN for 14 d), N = 27	To determine optimal P intake in PN in premature neonates	The low P intake showed signs of phosphate depletion (hypercalciuria, hypophosphatemia, and absence of phosphaturia). The high P intake group did not have signs of P depletion; however, they had high urinary cyclic adenosine monophosphate excretion and marked phosphaturia, suggesting secondary hyperparathyroidism. The moderate P intake group had evidence of neither phosphate depletion nor secondary hyperparathyroidism.	Used a very low Ca dose; the Ca:P mg:mg (mol:mol) ratios were 1.1:1 (0.84:1) in the low group, 0.8:1 (0.65:1) in the moderate group, and 0.56:1 (0.44:1) in the high group
Koo, 1987[47]	RCT PN with Ca and P at 5 mmol each vs 20 mmol each; standard vitamin D	Near-term infants (37.4 ± 0.5 wk) given PN for up to 6 wk, N = 18	To determine Ca and P homeostasis in infants receiving high vs low Ca and P intakes	The high Ca and P intake group had stable vitamin D concentrations. Tubular reabsorption of P was <90%. In the low Ca and P intake group, vitamin D concentrations were higher and tubular reabsorption of P was >90%.	
Aiken, 1986[48]	RCT PN containing low Ca (0.55 mEq/kg per day) and P (0.44 mEq/kg per day) vs high Ca (1.08 mEq/kg per day) and P (0.89 mEq/kg per day)	Infants <1500 g birth weight who received PN from 10 to 30 d of life, N = 15	To compare the effects of 2 different Ca and P regimens in VLBW infants after 10 d of life	Infants given the low Ca and P regimen had lower plasma and urine phosphate but similar urine Ca excretion to those given the high Ca and P regimen.	Urinary excretion of Ca and P was measured through the use of untimed samples; PN was given through peripheral intravenous lines; the investigators had to stop the low Ca and P regimen due to clinical issues in the infants
Chessex, 1985[49]	RCT PN containing P only from IVFE (~10 mg/kg per day) vs added P to 35 mg/kg per day Ca intake constant at 40 mg/kg per day	Infants <1500 g given PN for 3 d, N = 12	To determine the influence of P intake on calciuria in VLBW infants	The retention of P and the retention of Ca were both significantly higher in the group with additional phosphate	

Ca, calcium; IVFE, intravenous fat emulsion; LBW, low birth weight; OBS, observational study; P, phosphate; PN, parenteral nutrition; RCT, randomized controlled trial; VLBW, very low birth weight.

Table 7. GRADE Table, Question 3: What Are the Appropriate Calcium Intake and Calcium-Phosphate Ratios in PN for Optimal Neonatal Bone Mineralization?

Comparison	Outcome	Quantity, Type Evidence, Reference No.	Finding	GRADE	Overall Evidence GRADE
Ca:P ratios 1.3:1, 1.7:1 vs 2:1 (mg:mg)	Ca and P retention	1 RCT[42]	Ratio of 1.7:1 is superior	Moderate	Moderate
Ca:P ratios 1.1:1 mg:mg (0.84:1 mol:mol) vs 0.8:1 mg:mg (0.65:1 mol:mol) vs 0.56:1 mg:mg (0.44:1 mol:mol)	Optimal P intake	1 RCT[46]	Ratio of 0.8:1 was superior	Low	
Ca 45 mg/kg per day vs 75 mg/kg per day (fixed Ca:P ratio 1.7:1 mg:mg)	Bone strength	1 RCT[38]	Higher Ca dose is superior	Moderate	
Ca 64 mg/kg per day vs Ca 76 mg/kg per day (fixed Ca:P ratio ~1.1:1 mg:mg)	Ca and P retention and bone mineral content	1 RCT[41]	Higher Ca dose is superior	High	
Ca doses 36–76 mg/kg per day (fixed Ca:P ratio 1.7:1 mg:mg)	Ca and P retention	1 OBS[44]	76 mg/kg per day is superior	Moderate	

Ca, calcium; OBS, observational study; P, phosphate; RCT, randomized controlled trial.

Question 5. What are the clinical (infection, catheter occlusion) advantages or disadvantages of 2-in-1 compared with 3-in-1 PN admixtures?

Recommendation: We suggest that there is no clinical difference in infectious complications between the two PN delivery systems; 3-in-1 formulations administered in the homecare setting may increase the risk for catheter occlusion and shorten catheter lifespan.

GRADE: Weak (Tables 10 and 11)

Rationale: PN formulations are administered as either a dextrose–amino acid formulation (2-in-1) or a 3-in-1 formulation (amino acids, dextrose, and IVFE in 1 container). IVFE is administered separately as a piggyback infusion when prescribed as part of a 2-in-1 PN admixture. Advantages and disadvantages of each PN system have been identified. Many institutions embrace the 3-in-1 formulation because of perceived benefits related to compounding efficiency, less risk of contamination during administration, and potential cost savings. The primary drawback of this system is that it requires a larger pore size filter (1.2 μm) and precludes the use of a 0.22-μm filter, which eliminates a greater amount of particulate matter including some bacteria. The 3-in-1 system also suffers from a higher risk for emulsion destabilization from inappropriate concentrations of nutrients as well as a greater incidence of medication incompatibility with the fat emulsion portion of the admixture. Only 2 clinical trials have evaluated the differences between the 2 delivery systems in a controlled clinical environment. One study demonstrated that both systems were comparable with respect to the risk for microbial growth when administered over 24 hours.[60] A second trial suggested that 3-in-1 formulations administered in the pediatric home PN population were associated with more catheter occlusion and a shortened catheter lifespan.[61] Further controlled clinical trials must be conducted before one delivery system is identified as being superior over the other.

Question 6. What macronutrient dosing limits are expected to provide for the most stable 3-in-1 admixtures?

Recommendation: We recommend that total nutrient admixtures maintain final concentrations of amino acid ≥4%, monohydrated dextrose ≥10%, and injectable lipid emulsion ≥2% to be more likely to remain stable for up to 30 hours at room temperature (25°C) or for 9 days refrigerated (5°C) followed by 24 hours at room temperature.

GRADE: Strong (Table 12)

Rationale: Administering PN using 3-in-1 or TNA was first described by Solassol et al[62] in 1974. This system of combining amino acids, dextrose, IVFE, electrolytes, vitamins, and trace elements in a single container is widely used in hospital and home environments. This combination of many chemical entities has a high potential for chemical and physicochemical interactions that may result in problems with both short-term and long-term stability.[11,27,63]

The United States Pharmacopeia (USP) is responsible for creating official monographs and standards for drug manufacturing. Not until 2004 did the USP finally issue detailed specifications (ie, USP Chapter <729>) for lipid globule size limits and the appropriate instrumentation to define them related to lipid emulsion stability.[64] The emulsion refers to the many individual fat droplets that are carefully dispersed in the continuous (water) phase. The stability of lipid injectable emulsions is influenced by many factors including pH, temperature, free fatty acid concentrations, and lipid globule size. Two criteria are proposed by the USP for evaluating lipid stability of commercially prepared injectable lipid emulsions from the manufacturer: mean droplet size (MDS) and the population of

Table 8. Evidence Summary, Question 4: What Are the Clinical Advantages or Disadvantages of Commercially Available Premade ("Premixed") Multichambered PN Formulations Compared With Compounded PN Formulations?

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Pontes-Aruda, 2012[50]	RCT PreMCB, OOFE (n = 202) COM1, OOFE (n = 103) COM2, MCT/LCT (n = 101)	Critically ill, n = 406	To determine the impact of PN delivery system on the incidence of BSI over 28-day observation period	BSI COM1 + COM2 (46/204, 22.5%) vs PreMCB (34/202, 16.8%), $P = 0.03$ BSI/1000 catheter days COM1 + COM2 = 13.2/1000 vs PreMCB 10.3/1000, $P < 0.0001$ Days to start PN COM1 = 10, COM2 = 10 vs PreMCB, $P < 0.001$	Limitation with study findings: • No information on compounding standards used by facilities • Fat emulsions not available in the United States (ie, OOFE and MCT/LCT FE)
Mercaldi, 2012[51]	Retrospective evaluation of Premier Perspective Database	All hospitalized patients receiving PN from January 2005 through December 2007	Investigate whether different PN delivery systems could be identified in a hospital claims database	Data suggested that COM PN is associated with higher risk for BSI than PreMCB OR = 1.47 (95% CI, 1.22–1.61) in GI surgery patients OR = 1.49 (95% CI, 1.10–1.78) in oncology patients OR = 1.3 (95% CI, 1.08–1.41) in critical care patients	Limitation of study findings: • Lack of risk factors related to infection (ie, number of VADs, location of VADs, severity of illness, lack of estimate of the rate of BSI per catheter day)
Lenclen, 2006[52]	Retrospective evaluation of CUST vs STD PN	Premature neonates <32 wk gestation receiving STD PN (n = 20) in 2003 vs CUST PN (n = 20) in 2001	To evaluate the impact of changing from CUST to STD PN formulations	Intakes of AA and CHO were higher in STD group at day 3 (1.5 vs 0.9 g/kg per day AA, $P = 0.0001$; 10.7 vs 9.6 g/kg per day CHO, $P = 0.002$) Ca:P ratios were better balanced in the STD group at day 3 (1.35 vs 10 mg/mg, $P < 0.001$) No differences in weight variation at days 3 or 8, and no differences in growth at days 14 and 28	Comment: CUST PN was prepared by nursing staff under a LAFH vs STD PN prepared in a sterile isolator in the pharmacy compounding area.
Krohn, 2005[53]	Retrospective record review	Pediatric ICU patients aged 3 months to 18 years (N = 46)	To evaluate the use of STD PN formulations in a pediatric ICU over 8 months	226 prescriptions were written for STD PN; 111 prescriptions were written for CUST PN Na and P intakes were lower in CUST vs STD PN patients <10 kg (Na 1.5 vs 4.2 mmol/kg); (P 0 vs 1.1 mmol/kg) P was not given in 20 of 57 CUST PN Na was not included in 8 of 57 CUST PN 54% of patients receiving STD PN required nutrient modification	Limitation of study findings: • Lack of demographic data on patient population • Only descriptive results, no statistical analysis performed Comment: • STD PN formulations were originally prepared by the hospital pharmacy but modification of STD PN was performed by nursing staff under LAFHs on the ward. • CUST PN formulations were prepared by nursing staff under LAFHs on the ward
Yeung, 2003[54]	Retrospective record review	Newborn infants <33 wk gestation receiving STD PN between 2000 and 2001 (n = 27) vs infants receiving CUST PN between 1999 and 2000 (n = 31)	To evaluate the difference in nutrient intakes and biochemical responses as a result of receiving STD vs CUST PN between day 2 and day 7 of life	STD PN infants received significantly more protein each day and for a cumulative total during the first week of life (13.6 vs 9.6 g/kg, $P < 0.05$) STD PN infants received more P (1.25 vs 0.95 mmol/kg) and Ca (1.25 vs 0.95 mmol/kg, $P < 0.02$) from days 4 to 7 but less Mg (0.2 vs 0.3 mmol/kg, $P = 0.21$)	Comment: • Standardized PN formulations were commercially batched produced • CUST PN formulations were produced by the pharmacy department. • Estimated cost of STD PN was $88 AUD per bag Australian dollars vs CUST PN at $130 AUD per bag.

(continued)

Table 8. (continued)

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Hayes, 2000[55]	OBS	Patients receiving STD PN (992 patient days) vs CUST PN (306 patient days) during a 4-month period	To assess the effect that CUST PN and STD PN formulations have on laboratory test results (ie, Na, K, CO_2, Mg, P, Cl)	STD PN patients had a higher percentage of laboratory values within normal limits vs CUST PN patients (73% vs 67%, $P = 0.005$)	Limitations of the study: • No description of patient population • No description of who decided, and how the decision was made, regarding which patients received STD vs CUST PN • It appears that abnormal serum CO_2 concentrations accounted for the greatest difference in abnormal laboratory values between groups • The percentage of subtherapeutic laboratory values was higher with STD PN for Mg (20.5 vs 8.8%) and P (21.2 vs 9.6%) but electrolyte supplementation was not mentioned • Multielectrolyte cocktails were used (ie, Lypholyte), and these contain $CaCl_2$ and $MgCl_2$, but incompatibilities were not mentioned
Beecroft, 1999[56]	OBS	Newborn infants (gestational age 29 wk; median birth weight 1080 g) receiving PN within a tertiary level neonatal unit over a 4-wk period	To investigate the potential for using premixed STD PN formulations by evaluating the frequency with which CUST PN prescriptions deviated from computer-recommended PN formulations	121 of 148 (82%) PN prescriptions deviated from PN formulations based upon computer-recommended feeding regimens The number of deviations per 148 PN prescriptions in relation to specific nutrients included: • CHO 91 (61%) • AA 11 (7%) • Fat 0 (0%) • Na 77 (52%) • K 14 (9%) • P 78 (53%) • Ca 36 (24%) Abnormal serum laboratory results included: • Na 13% • K 53% • Ca 4% • P 69%	Limitations of study: • Only included a comparison of CUST PN formulations against an STD PN formulations recommended via a computer program (ie, KabiPN)

AA, amino acid; AUD, Australian dollars; BSI, bloodstream infection; Ca, calcium; CHO, carbohydrate; CI, confidence interval; Cl, chloride; CO_2, bicarbonate; COM, compounded PN group; CUST, customized; GI, gastrointestinal; ICU, intensive care unit; K, potassium; LAFH, Laminar airflow hoods; MCT/LCT FE, medium-chain triglyceride/long-chain triglyceride fat emulsion; Mg, magnesium; Na, sodium; OBS, observational study; OOFE, olive oil fat emulsion; OR, odds ratio; P, phosphate; PN, parenteral nutrition; PreMCB, premixed multichamber PN bag; RCT, randomized controlled trial; STD, standardized; VAD, venous access device.

Table 9. GRADE Table, Question 4: What Are the Clinical Advantages or Disadvantages of Commercially Available Premade ("Premixed") Multichambered PN Formulations Compared With Compounded PN Formulations?

Comparison	Outcome	Quantity, Type Evidence, Reference No.	Finding	GRADE	Overall Evidence GRADE
Premade vs compounded PN	BSI	1 OBS[50] 1 OBS[51]	Premade better	Low	Low
Standard vs customized PN	Nutrient intake	3 OBS[52-54]	Standard better	Low	
	Laboratory measures	1 OBS[55]	Standard better	Low	
	Deviation from a standard	1 OBS[56]	Customized better	Low	

BSI, bloodstream infections; OBS, observational study; PN, parenteral nutrition.

large-diameter fat globules (>5 μm) for the "tail" of a droplet distribution curve. MDS must not exceed 500 nm, while the large-diameter tail of the lipid globule size distribution (GSD) cannot exceed 0.05%. Measurements of the large-diameter tail are expressed as the percentage (volume-weighted) of fat >5 μm, also referred to as the PFAT5. The distribution of lipid globules throughout the emulsion is the most important aspect from a clinical perspective because this indicates the final safety of the formulation with respect for pulmonary embolism.[65] The specified limit of 5 μm emanates from physiologic evidence as it represents the minimum size of a lipid droplet capable of obstructing the smallest pulmonary capillaries after infusion into a large central vein. The 5-μm limit is also an important determinant of the stability of the emulsion system. For injectable lipid emulsions composed of pure long-chain triglycerides ranging in concentrations from 10% to 30%, it has been demonstrated that the PFAT5 is universally <0.05%. Thus, PFAT5 levels >0.05% reflect the onset of or continuing lipid destabilization.

Of equal importance, USP Chapter <729> specifies that 2 methods of analysis must be used to measure particle or droplet size.[66] Method 1 employs the use of dynamic light scattering (DLS) to measure the MDS of injectable lipid emulsions. This technique is extremely valuable for measuring the homogeneity of lipid droplets dispersed throughout the emulsion. Unfortunately, this type of technique often lacks sensitivity to subtle changes in droplet size that occur in the large-diameter tail of the GSD. Destabilization of injectable lipid emulsions will create increased droplet/globule populations of the large-diameter tail of the GSD. Changes identified in the large-diameter tail with PFAT5 will have practically no detectable effect on the MDS as measured by DLS. As a result, method 2 uses light obscuration or extinction with a single-particle optical sensing (LE/SPOS) technique to report the number of particle or globule counts as a function of the geometric mean diameter of droplets over a desired range (2–25 μm).[67] In simpler terms, this instrument measures a change in light intensity between identically sized reference particles used to calibrate the machine and the passage of dispersed lipid droplets through an optical sensing zone. In 1995, Driscoll et al[68] evaluated the stability of 45 extemporaneously prepared TNA admixtures with DLS and LE/SPOS techniques. Only after the DLS data were stratified according to the corresponding LE/SPOS value of PFAT >5 μm was it determined that unstable emulsions were linked with the presence of >0.4% of the fat particles at >5 μm. Sensitivity testing revealed that a TNA with >0.4% of its total fat concentration present as particles >5 μm would likely destabilize or "crack" 85% of the time, whereas a TNA with <0.4% of its total fat concentration present as particles of >5 μm would be stable 88% of the time. In terms of actual results, unstable emulsions were identified by visual evidence, such as free oil droplets at the surface of the formulation, only 65% of the time (34 of 52 TNAs). Commercially available IVFEs in the United States are stabilized with egg yolk phosphatides that provide both a mechanical and an electrical barrier to particle coalescence. This phospholipid mixture imparts a negative surface charge on the emulsified lipid particles and prevents coalescence by inducing electrostatic repulsion between the particles. The primary fatty acid components in the phospholipid mixture include palmitic, oleic, stearic, and linoleic acids, in decreasing order of concentration. Instability occurs when there are ion interactions, variations in ionic strength, and pH changes occurring in the aqueous phase of the emulsion. Any decrease in pH value will alter the electronegativity (zeta potential), and the emulsion becomes more unstable. Injectable lipid emulsions are most stable at their manufactured pH (~6–9). The addition of dextrose, which is acidic, can contribute to TNA instability. Electrolytes, especially the positively charged divalent cations calcium and magnesium, and trivalent ferric ions neutralize the negative charge on the surface of the lipid particle

Table 10. Evidence Summary, Question 5: What Are the Clinical (Infection, Catheter Occlusion) Advantages or Disadvantages of 2-in-1 Compared With 3-in-1 PN Admixtures?

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Erdman, 1994[61]	Retrospective record review	22 pediatric patients receiving home PN in whom 28 central venous catheters (4F single-lumen silicone) had been placed	To evaluate the impact of separate IVFE administration vs 3-in-1 PN on the incidence of catheter occlusion	8 catheters had been used exclusively for 3-in-1 PN and 7 catheters used exclusively for separate IVFE All 8 of the 3-in-1 catheters were occluded at removal; 5 of 7 other catheters were patent and in use at the time of study 2 of 7 occluded catheters were from the same patient and were not retrieved for inspection Median catheter survival was 70 d for the 3-in-1 group vs 290 d for the separate IVFE group ($P = 0.025$) Deposits recovered from 3-in-1 catheters were insoluble in urokinase, acetone, or 0.1 N HCl; however, deposits were partially soluble in 0.1 N NaOH Only the final dextrose concentration of PN was significantly different between the 2 groups (14.5 vs 18.8%, $P = 0.01$)	Limitations of the study include: • Observational and descriptive • All PN formulations were compounded on a weekly basis and refrigerated 1–7 d in patient's home • Conducted only in pediatric patients • No inline filter used • Small caliber of pediatric catheters may have contributed to occlusions
Vasilakis, 1988[60]	OBS	49 patients receiving 2-in-1 PN with separate IVFE and 3-in-1 PN	To determine if IVFE can be safely added to 2-in-1 PN when delivered over 24 h without becoming contaminated with bacteria or fungi	200 PN fluid/IVFE cultures obtained from 49 patients: 88 samples from 2-in-1 PN with separate IVFE and 112 samples from 3-in-1 PN 166 (83%) cultures were negative and 34 (17%) were positive Of the 34 positive cultures, 15 of 88 (17%) were from the 2-in-1 PN and 19 of 112 (17%) were from 3-in-1 PN	Limitations of the study include: • Group allocation not randomized, unknown number of patients in each group, absence of patient demographic data, small sample size can create type II error

IVFE, intravenous fat emulsion; OBS, observational study; PN, parenteral nutrition.

and lead to loss of the electrostatic and mechanical barrier created by the emulsifier. Amino acids are considered to provide a protective effect by enhancing the admixture's buffering effect and reducing the propensity for coalescence. Other additives including medications, electrolytes, vitamins, and trace elements may also affect stability of the TNA formulation. Given the numerous permutations in the concentration of TNA ingredients, predicting the stability of any single TNA is difficult. The stability of the TNA is also dependent on the container and storage conditions including light exposure and temperature.[63,69-71] Careful attention to detail is necessary when trying to extrapolate study findings to the stability of a

Table 11. GRADE Table, Question 5: What Are the Clinical (Infection, Catheter Occlusion) Advantages or Disadvantages of 2-in-1 Compared With 3-in-1 PN Admixtures?

Comparison	Outcome	Quantity, Type Evidence, Reference No.	Finding	GRADE	Overall Evidence GRADE
2-in-1 PN vs 3-in-1 PN	Catheter occlusion	1 OBS[61]	2-in-1 better	Low	Low
	PN contamination	1 OBS[60]	No difference	Low	

OBS, observational study; PN, parenteral nutrition.

specific TNA. In the study by Driscoll et al, 45 different TNA admixtures were evaluated with final concentrations of monohydrated dextrose ranging from 5% to 20%, amino acids ranging from 2.5% to 7%, and injectable lipid emulsions ranging from 2% to 5%.[74] In addition, the micronutrient composition included monovalent cations (sodium and potassium) in the range of 0–150 mEq/L, divalent cations (calcium and magnesium) in the range of 4–20 mEq/L, and trivalent cations (ferric ions in iron dextran) in the range of 0–10 mEq/L. Close inspection of the data reveals that in general, TNA admixture final concentrations must be at least 10% monohydrated dextrose, 4% amino acids, and 2% injectable lipid emulsions to ensure admixture stability. However, monovalent, divalent, and trivalent cations clearly influence the final admixture stability, with divalent concentrations between 16 and 20 mEq/L requiring final concentrations of monohydrated dextrose >10% and amino acids >4% to prevent lipid destabilization.[72] Because trivalent cations appear to have the highest potential for creating instability in TNAs, it is currently recommended that iron dextran (ie, ferric ions) not be incorporated into these formulations.[74]

Most investigations conducted to study the physicochemical stability of TNAs evaluated specific amino acid and/or IVFE products vs dosing or concentration ranges of macronutrients or assessed the stability of TNAs prescribed for patients.[68,73-79] All of these investigations assessed IVFE products made from long-chain triglycerides. Driscoll et al evaluated the physicochemical stability of TNAs prepared with an IVFE made from both medium-chain and long-chain triglycerides, which produced more stable TNAs than long-chain triglycerides.[70,80]

The safety of providing TNAs encompasses more than the stability of the formulation. Prolonged storage and/or light exposure may result in degradation or bioavailability of some components, especially vitamins. Furthermore, long-term storage may promote bacterial growth.[73] The limits provided in this recommendation are merely a guide, and specific stability data on an individual TNA formulation should be sought.

Question 7. What are the most appropriate recommendations for optimizing calcium (gluconate) and (Na- or K-) phosphate compatibility in PN admixtures?

Recommendation: We cannot make a recommendation due to the multiple variations in amino acid concentrations, PN volume, pH, presence or absence of fat emulsion, and the amounts of other minerals (eg, magnesium). We suggest that published graphs for specific products provide adequate guidance; however, no evidence indicates that these formulations remain stable for >24–48 hours.

GRADE: Weak (Table 13)

Rationale: Calcium and phosphate solubility depends on a number of factors, including the final amino acid concentration, temperature, pH, the mixing sequence, 2-in-1 vs 3-in-1 mixtures, and the relative amounts of the calcium and phosphate ions. Solubility curves have been developed and validated that provide the best guidance in determining the maximum amount of calcium and phosphate to be added to any particular PN solution.[81] Amino acid solutions >1% with added cysteine at 40 mg/g of amino acid appear stable for 30 hours with a calcium concentration of 60 mg/dL and phosphorus at 46.5 mg/dL. Studies validating the stability of PN solutions beyond 48 hours are lacking.

Question 8. What micronutrient contamination is present in parenteral stock solutions currently used to compound PN admixtures?

Recommendation: We suggest that, given the level of mineral contamination found in parenteral stock solutions used to compound PN admixtures, practitioners purchase products that accurately describe levels of contamination and also take that exposure into account when recommending or reviewing trace element dosing.

GRADE: Weak (Table 14)

Rationale: Trace element contamination is found in most parenteral components expected to be free of these minerals, with little additional contamination found from simulated and manual compounding.[89-96] Amounts of contamination can vary between manufacturers and from lot to lot within a manufacturer's product.[92,94,96] At least a dozen minerals (from arsenic to zinc) have been identified as contaminants. Although the problem with aluminum toxicity has been partially addressed by the United States Food and Drug Administration (FDA), significant variation in aluminum content was found between manufacturers, vial size, and concentrations. Statistically significant differences in aluminum content of PN solutions before and after its minimization were also seen.[97,98] The trace elements chromium and zinc are the most frequently measured

Table 12. Evidence Summary, Question 6: What Macronutrient Dosing Limits Provide for the Most Stable 3-in-1 Admixtures?

Author, Year, Reference No.	Study Design	Macronutrients	Study Objective	Results	Comments
Driscoll, 2006[80]	In vitro	Clinically relevant concentrated TNAs prepared with a concentrated AA injection, concentrated dextrose, and IVFE of 50:50 mixture of MCT and LCT	To study the physicochemical stability of highly concentrated TNAs for fluid-restricted patients	Concentrated TNA formulations stable for 30 h at room temperature No significant changes in physicochemical stability by DLS or LE-SPOS All TNAs with mean droplet size <0.5 μm No significant increase in globule size distribution; PFAT5 measurements <0.05% Large-diameter fat globules decreased over time	TNAs designed to provide protein 1.5 g/kg per day and energy 25 kcal/kg per day for adults weighing 40–80 kg with final volumes of 843–1562 mL Final concentrations (g/L) of macronutrients: AAs (Aminoplasmal) 71.2–76.8, dextrose 196.9–213.2, IVFE 24.9–26.9 Fixed amount of electrolytes, vitamins, and minerals added to each TNA Stored in EVA bags TNAs prepared with MCT appear more stable than those prepared with LCT Included analysis of large-diameter tail of the emulsion
Driscoll, 1995[68]	In vitro	Clinically relevant TNAs prepared with AA injection, dextrose, soybean oil IVFE	To examine the influence of 6 factors on the stability of 45 clinically relevant intravenous nutritional dispersions under typical hospital conditions by using a balanced fractional design	Trivalent cation concentration only variable that affected TNA stability Emulsions with >0.4% of the initial fat concentration consisting of particles >5 μm in diameter are likely to become unstable Unstable TNA visually evident 65% of time	Factors studied: AAs-Aminosyn II (2.5%–7%), dextrose (5%–20%), IVFE-Liposyn II (2%–5%), monovalent cations (Na and K, 0–150 mEq/L), divalent cations (Ca and Mg, 4–20 mEq/L), trivalent cations-iron dextran (elemental iron, 0–10 mg/L) Other TNA additives: heparin sodium 3000 units, phosphate 15 mmol, trace elements, multivitamins Concentration of trivalent cations should be ≤2.95 mg/L to ensure stability of the TNA (clinically conservative maximum dose of 2 mg/L) TNA with >0.4% of fat particles as particles >5 μm likely to crack 85% of time; if <0.4% of fat particles as particles >5 μm, stable 88% of time
Deitel, 1992[79]	In vitro	Clinically relevant, energy-dense TNAs	Determine whether the emulsion in a more calorie-dense (0.9 non-protein kcal/mL) TNA remained stable for longer storage periods of 4 wk refrigerated +2 d at room temperature	TNA stable for 28 d at 4°C followed by 2 d at 22°C Visual examination: no creaming or color change Light microscopy: mean diameter of lipid particles <3 μm through study Electron microscopy: fat droplet size increased slightly after storage at room temperature; after 30 d storage mean diameter 0.36 ± 11 μm No significant change in pH, osmolality, or fatty acid profile over study period	Concentration of macronutrients in TNA: AAs (FreAmine III-B. Braun) 3.9%, dextrose 19.2%, IVFE (Soyacal, Alpha Therapeutic) 1.9% Electrolytes, trace elements, multivitamins, heparin, ranitidine, and iron dextran added at time of preparation TNAs stored in EVA bags. IVFE, Soyacal (Alpha Therapeutic), not available in United States

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Table 12. (continued)

Author, Year, Reference No.	Study Design	Macronutrients	Study Objective	Results	Comments
Tripp, 1990[78]	In vitro	Clinically relevant TNAs prepared with a dual-chamber bag system with AAs with and without electrolytes + dextrose + safflower-soybean oil fat emulsion.	To study the stability of a TNA prepared from dextrose and AA injections commercially packaged in a dual-chamber container and a safflower-soybean oil fat emulsion after storage for 1 d and 10 d	TNAs stable after 24 h at room temperature TNAs stable after 9 d at 5°C followed by 1 d at room temperature Creaming observed at end of storage for majority of TNAs pH value, emulsion particle size, weight % of oil particles >5 μm in diameter, AA, and dextrose concentrations essentially unchanged over study periods	Range of concentrations of macronutrients in TNAs studied. Amino acids (Aminosyn II, Hospira) 2%–4%; dextrose 4%–20%; IVFE (Liposyn II, Hospira) 2%–8% Electrolytes and trace elements added at time of preparation. Multivitamins added prior to 24 h storage at room temperature Safflower-soybean oil fat emulsion (Liposyn II, Hospira) no longer available in United States Nutrimix (B. Braun) dual-chamber bag system no longer available in United States
Deitel, 1989[77]	In vitro	Clinically relevant TNA	To find out how long the TNA remains stable while in refrigerated storage	TNA stable with respect to liposome aggregation for 14 d at 4°C followed by 2 d at 22°C Visual inspection: no creaming. Light microscopy: liposomes >5 μm increased over 16 d; mean 3.9 ± 2.4/20 HPP Electron microscopy: particle size increased over 16 d; none exceeded 2 μm in diameter Coulter counter: liposome size increased; 99.8% <1.9 μm in diameter pH: 5.5 ± 0.1; trend to decrease Osmolality: 1472 ± 31 mOsm/kg; trend to increase	Concentrations of macronutrients in TNA: AAs (Vamin-N, Fresenius Kabi) 3.4%, dextrose 16.1%, IVFE (Intralipid, Fresenius Kabi) 1.6% Electrolytes, trace elements multivitamins, heparin, ranitidine, and iron dextran added at time of preparation Storage container not described Amino acid injection studied, Vamin-N, Fresenius Kabi not available in United States
Sayeed, 1987[75]	In vitro	Clinically relevant TNAs prepared with safflower oil–soybean oil IVFE, AA injection, and dextrose	To study the compatibility of a safflower oil–soybean oil emulsion with dextrose and AA injection with or without electrolytes in total nutrient admixtures	Safflower oil–soybean oil emulsion in TNAs stable for 1 d at room temperature, 2 d at 5°C + 2 d at 30°C and 9 d at 5°C + 1 d at room temperature Visual inspection: creaming present but disappeared with gentle shaking; no free oil droplets or yellow oily streaks pH: 5.5–5.9 reflecting pH of AA product Zeta potential: essentially unchanged Particle size (volume-weighted mean values): TNA made with IVFE 10% <0.35 μm; TNA made with IVFE 20% 0.38–0.44 μm; essentially unchanged; mean particle values initially and at days 1, 3 and 10 unchanged from initial IVFE No change in weight percentage of oil globules >5 μm Little or no change in dextrose and AA potency over study period	Concentration of macronutrients in TNA: AAs (Aminosyn II, Hospira) 2.3%–4%, dextrose 3.3%–23.3%; IVFE (Liposyn II, Hospira) 2%–6.7% Electrolytes and trace elements added at time of preparation. Multivitamins added prior to 1-d storage at room temperature TNAs stored in EVA bags IVFE studied but not available in United States: Liposyn II, Hospira

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Table 12. (continued)

Author, Year, Reference No.	Study Design	Macronutrients	Study Objective	Results	Comments
Sayeed, 1987[76]	In vitro	Clinically relevant TNAs prepared with various combinations of different AA injections, IVFE products, and dextrose	To study the stability of 4 IVFE products, AA injections, and dextrose in TNA	TNAs studied generally stable after 24 h at room temperature and after 9 d at 5°C followed by 1 d at room temperature Visual appearance: 39/43 TNA with uniform "milk-like" appearance; 4 with yellow streaks at 10 d but dispersed by gentle shaking No significant change in pH, zeta potential, osmolality after 1 or 10 d No substantial increase in particle-size distribution (volume-weighted mean diameter values) during storage 1/43 TNA with substantial increase in particle-size measurement of oil globules (weight % of oil globules >5 μm) during storage at day 10	Range of concentrations of macronutrients in TNAs studied. Amino acids 1.1%–4.6%; dextrose 3.3%–28%; IVFE 2%–6.7% Amino acid injections studied: Travasol, Baxter; FreAmine III, B. Braun; Novamine, Hospira; Nephramine, B. Braun; RenAmin, American Hospital Supply IVFEs studied: Intralipid, Fresenius Kabi; Travemulsion, Baxter; Soyacal, Alpha Therapeutic Electrolyte elements added at time of preparation. Multivitamins added prior to 24 h storage at room temperature TNAs stored in EVA bags. Authors unable to explain why 4 TNAs showed evidence of instability Analysis of AA and dextrose content over study period not conducted IVFE studied but not available in United States: Liposyn II, Hospira; Travemulsion, Baxter; Soyacal, Alpha Therapeutic; Novamine, Hospira; RenAmin, American Hospital Supply
Barat, 1987[73]	In vitro	Clinically relevant TNAs prepared with various AA injection products, dextrose, and a soybean oil IVFE	To compare the physicochemical stability of 10 TNA systems varied by the AAs injection used	TNAs physically stable for 14 d at 4°C followed by 4 d at ambient temperature All TNAs had creaming at days 0 and 18 but dispersed with gentle agitation No significant change in mean diameter of particles during study, 95% particles <6 μm in diameter pH: >5.7 with no appreciable change Osmolality: no significant change Peroxides: none found	TNAs prepared with AA, dextrose 70%, and IVFE (Soyacal, Alpha Therapeutic) 20% mixed volume ratios 1:1:1 AA products used: Travasol 8.5% & 10% (Baxter), Aminosyn 8.5% & 10% (Hospira), FreAmine III 8.5% and 10% (B. Braun), Aminosyn RF 5.2% (Hospira), HepatAmine 8% (B. Braun), FreAmine HBC 6.9% (B. Braun), and NephrAmine 5.4% (B. Braun) Other additives: electrolytes, heparin, trace elements, multivitamins, folic acid, vitamin B complex Soyacal 10% (Alpha Therapeutic) no longer available in United States
Sayeed, 1986[74]	In vitro	Clinically relevant TNAs prepared with AA injection, dextrose, and safflower oil–soybean oil IVFE	To study the compatibility and safety of a safflower oil–soybean oil IVFE emulsion with AAs and dextrose in TNAs	All TNAs stable over study time 1 d at room temperature, 2 d at 5°C then 1 d at 30°C or 9 d at 5°C then 1 d at room temperature Visually stable with no creaming Particle size essentially unchanged Zeta potential—good stability Dextrose and AA concentrations did not change	TNAs prepared with AAs (Aminosyn II (Hospira), dextrose, and IVFE (Liposyn II; Hospira) Electrolytes and trace elements added at time of preparation Multivitamins added prior to 1-d storage at room temperature Animal testing-TNA administered to beagles to assess toxicity—no adverse events Liposyn II (Hospira) no longer available in United States

AA, amino acid; DLS, dynamic light scattering; EVA, ethylene vinyl acetate; IVFE, intravenous fat emulsion; LCT, long-chain triglyceride; LE-SPOS, light extinction with single-particle optical sensing; MCT, medium chain triglyceride; PFAT5, percentage of fat globules >5 μm diameter; TNA, total nutrient admixture.

Table 13. Evidence Summary, Question 7: What Are the Most Appropriate Recommendations for Optimizing Calcium (Gluconate) and (Na- or K-) Phosphate Compatibility in PN Admixtures?

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Migaki, 2012[82]	In vitro	Neonatal, 235 PNs	Evaluation of various combinations of Ca:P in 8 different combinations of AAs using Ca chloride	When AA concentration ≥3%, Ca concentrations of 12.5 mmol/L were compatible with P concentrations of 15 mmol/L	Solubility evaluated at 24 h, Trophamine without cysteine was used, no IVFEs involved, compatibility was only evaluated visually
MacKay, 2011[81]	In vitro	Pediatric formulations, 39,019 PNs studied	Plot the Ca:P concentrations against the standard saturation curves, which were published in 1989, to assess the validity of the curves; then extrapolate the data to predict solubility	Various AA concentrations with and without cysteine and Ca:P ratios were plotted against the saturation curves and new curves were generated	2-in-1 and Y-site with IVFEs; evaluations for stability were tested 30 min after mixing and no further testing was performed; visual inspection only
Joy, 2010[83]	In vitro	Neonatal formulations, 12 PNs	Evaluate to Ca:P solubility of 3 different AA concentrations in a 5% dextrose product	PN solutions with AA concentration <3% and a dextrose concentration of 5% should not contain >2.5 mmol of calcium (as gluconate) and no more than 15 mmol P	Solubility studied for no more than 48 h without IVFE
Singh, 2009[84]	In vitro	Neonatal formulations, 8 PNs	Evaluation of effect of 4 concentrations of AA and 2 levels of dextrose on Ca:P solubility along with the effect of temperature	AA concentrations >3% required for solubility of 60 mg/dL Ca and 46.5 mg/dL P	Solutions evaluated at intervals up to 24 h only
Parikh, 2005[85]	In vitro	Neonatal, 8 PNs	Evaluation of the effect of 5 different AA concentrations and 2 dextrose concentrations on a fixed amount of 60 mg/dL of Ca (as gluconate) with 46.5 mg/dL of a dibasic phosphate salt with cysteine added	Ca:P in the solution with an AA concentration <0.5% and dextrose concentration of 5% was not stable	Solubility studied for no more than 30 h, AA formulations contained cysteine, no IVFEs were included
MacKay, 1996[86]	In vitro	Pediatric formulations, 22 PNs	Determine the precipitation limits for Ca:P in 2 specialty AA solutions with varying AA concentrations	Solubility curves were plotted	Solubility studied for no more than 18 h, no limits or maximums were stated
Dunham, 1991[87]	In vitro	Neonatal, 88 PNs	Develop a solubility curve for Ca:P in 2 amino acid concentrations	Ca concentrations ranging from 5 to 60 mEq/L with phosphate concentrations ranging from 5 to 40 mmol/L in 1% and 2% AA concentrations	Solubility evaluated at 24 h, curve of compatibility was extrapolated
Venkataraman, 1983[88]	In vitro	Neonatal, 30 PNs	Evaluation of various combinations of Ca:P in 2 different combinations of AAs and dextrose	A maximum of 150 mg/dL of Ca could be safely added to a 2.5% AA, 10% dextrose solution containing 100 mg/dL of P at 48 h	Solubility demonstrated at 48 h

AA, amino acid; Ca, calcium; IVFE, intravenous fat emulsion; P, phosphate; PN, parenteral nutrition.

Table 14. Evidence Summary, Question 8: What Micronutrient Contamination Is Present in Parenteral Stock Solutions Currently Used to Compound PN Admixtures?

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Speerhas, 2007[97]	In vitro 50 samples from adult and pediatric/neonate PN solutions vs IV large-volume parenteral solutions as controls Comparison: PN Al vs calculated dose from manufacturer	2 separate reference laboratories used for sample analysis Outcome: amount of measured PN Al Findings: less than calculated	To directly measure the Al concentration in a select number of PN solutions and to compare this value with the calculated dose using the concentrations reported by the manufacturer	23 values used in statistical analysis. Only 2 adult PN solutions were equal to or exceeded the FDA threshold for measured Al exposure. Measured Al for all 6 pediatric and neonate solutions met or exceeded FDA threshold. This value was much lower than what had been estimated using the labeled Al concentration at expiration.	In PN solutions expected to have moderately high Al concentration, measured Al was far less than would be estimated by calculation using labeled concentrations of Al in each of the ingredients
Smith, 2007[98]	In vitro 10 each of neonatal, pediatric, and adult PN patient solutions were evaluated to quantify the Al content on the basis of the ingredients used at the author's institution. A recalculation was performed using the lowest Al containing ingredients to determine the extent of Al minimization possible for each PN solution	Compare: Quantified Al content of current PN solutions (neonate, pediatric, adult) vs calculated lowest amount possible	To quantify, through calculation, the Al content in common ingredients used to compound PN solutions and then explore opportunities to minimize Al content by changing manufacturer of the ingredients Outcome: Al content of solutions before and after minimization Findings: Increased amount (significant) of Al in PN compared with calculated minimization. Significant variability between manufacturers	Significant variation in Al content found between manufacturers, vial size, and concentrations. Statistically significant differences in the mean Al content of PN solutions before and after Al minimization were found within each sample of patients. Mean Al content reduced: •Neonate: 84.16–33.6 µg/kg per day •Pediatric: 16.24–3.66 •Adult: 4.58–2.31	Selecting products with low Al concentration may substantially decrease the amount of Al patients receive in PN Repackaging Ca gluconate in polyethylene vials in the U.S. would significantly reduce Al content in PN Excellent reference table of content of common ingredients used in PN—compiles 5 different manufacturers
Bohrer, 2005[103]	In vitro Arsenite and arsenate species in solutions of AA, salts, vitamins, SWFI, and IVFEs commercialized for IV administration measured with AAS	Compare: Amount of arsenic species measured in common components of PN vs expected (<0.1 mg/L) Outcome: Amount of arsenic species as measured	To measure arsenite, arsenate species, and total arsenic in solutions of AA, salts, vitamins, and IVFE commercialized for IV administration. Finding: Allowable limit exceeded in Ca gluconate, Na bicarbonate, and some vitamin preparations. Arsenic species found in all investigated formulations.	All investigated products were found to have arsenic as a contaminant, but only in Ca gluconate, Na bicarbonate, and some vitamin preparations did the total arsenic limit exceed the allowable amount. In IVFE, KCl, NaCl, and Na phosphate solutions, the only arsenic species present was arsenate. In Ca gluconate, glucose, Mg sulfate, and some AAs, the arsenic was divided 50% between both species.	Arsenic should not exceed 0.1 mg/L in products for IV administration. For contamination control, only plastic materials used.
Driscoll, 2005[71]	In vitro Products used in compounding clinically relevant infant and adult PN solutions from a single manufacturer were selected for study. These consisted of AA 10% (adult and pediatric), dextrose 70%, fat emulsion 20%, SWFI, electrolytes, TE-4, cysteine hydrochloride, MVI-12, MVI pediatric. Calculations based on maximum Al concentration at expiry reported on label of each product.	Compare: Al content of current PN products (Abbott, adult and neonate) vs exposure of no more than 5 µg/kg per day. Outcome: Amount of calculated Al exposure in typical PNs	To calculate the theoretical Al exposure associated with the products from a manufacturer in compliance with 2004 FDA industry mandate (Abbott) in clinically relevant nutrition support scenarios for infants and adults. Desired outcome for PN patients was to limit cumulative Al exposure to no greater than 5 µg/kg per day. Finding: Al exposure far exceeds clinical limits	To provide adequate amounts of macronutrients and micronutrients for adults and infants, the total Al exposure far exceeds clinical limits from the warning statement on package inserts. In adults, most Al is found in Ca gluconate and inorganic phosphate injections. In infant PN solutions, another major source is AA cysteine hydrochloride.	Data on Al concentrations supplied by Abbott and AAI-Pharma Minimization recommendations include using components packaged in plastic vials rather than glass when available, providing mineral supplements on alternate days, or replacing K phosphate with Na phosphate, but in many cases the authors state there are no appropriate substitutions if patient is in high-risk group, and reduction efforts should come from improved manufacturing techniques.

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Table 14. (continued)

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Advenier, 2003[104]	OBS 10 children aged 1.5–16 y, on cyclic home PN mean 6.5 d/wk (range, 4–7 d/wk) Components of the patient's PN, the PN solutions, and patient plasma samples at end of PN cycle	Compare: Al content of 10 pediatric patients' PN vs Al content of similar population 10 y prior Outcome: Amount of measured Al in above PNs	To determine the Al contamination of PN solutions and their components and to assess the Al status of children on long-term PN Finding: Al content significantly less than Al measured in similar population's PN 10 years prior	Mean Al concentration in PN = 1.6 μmol/kg per day. Highest Al amounts in TEs, Ca salts, K lactate, dipotassium phosphate, and AA solutions. In final PN solution, Ca additive provided about 50% of Al, TE 20%, followed by AA and dextrose. Serum Al and daily Al urinary excretion of the children remain greater than normal.	Reported in μmol, not μg/kg per day Al content significantly less than amount studied 10 y ago in same hospital unit, but same amount as study from 1995.
Bohrer, 2002[105]	In vitro Al contamination in 35 different commercial PN components products and quality grades, including AAs, electrolytes, glucose, IVFEs, vitamins, TEs, and albumin by AAS	Compare: Amount of Al measured in products used to compound PN vs expected (safety limit) Outcome: Amount of Al measured in different commercial products and quality grades	To investigate the contamination level of infusions and PN solutions commercialized in Brazil, including the contamination of substance (raw material) used in preparation Finding: Highest amounts of Al in additives cysteine, Na hydroxide, gluconate and lowest in macronutrients AA, glucose, IVFE	Al content varied with manufacturer. Highest contamination found in cysteine, Na hydroxide, vitamin C, biotin, gluconate, and Fe and Cr salts. Lowest in IVFE, apolar AAs, glucose, HCl, acetic acid, KCl, and heparin. Commercially, major contamination found in Ca gluconate, TEs, some vitamins, bicarbonate, phosphate salts, and heparin.	
Buchman, 2001[89]	Animal study 5 PN solutions (2 adult standard, 1 renal, 1 standard pediatric) and 28 PN components analyzed with mass spectrometry. N = 26 rats assigned chow/NaCl or PN × 14 d; tissues analyzed for heavy metal deposition	26 rats Comparison: Amount of heavy metal contamination in common PN formulations and pathologic organ deposition in rats vs expected	To measure the degree of heavy metal contamination in PN solutions and investigate whether this contamination is associated with organ deposition/damage in a PN animal model Outcome: Amount of micronutrient contamination in PN; animal organ deposition Finding: Significant heavy metal contamination found	Predominant sources of contaminants in PN were AAs (Al, As, Cr, Ge, Pb, Sn), dextrose (As, Ba, Cr, Sn), CaGlu (Al), K Phos (Al), IVFE emulsion (As, Sn), and vitamins (As). Significant variation found in contamination levels between various PN formulations and brand of constituents. Hepatic Cr and Pb, splenic Ba, Cr, Ge, Pb, Mn, and Sn were higher in PN rats. Histology = 50% PN rats with hepatic steatosis, 33%–50% with renal morphologic abnormalities.	Rats administered PN vs chow Rats housed under laminar flow. Means compared with Student's *t* test; Pearson's correlation also used. Authors state that Cr and Mn from PN may contribute to development of PN-associated nephropathy
Mouser, 1999[99]	OBS n = 4 infants, n = 7 children (age 1–12 y) receiving home PN A portion of PN that was infusing during the 24h urine collection was drawn from PN container and measured for Cr and Zn using atomic absorption spectrometry. Serum, urine, and PN Cr concentrations measured at baseline and 4–6 months later. In children, serum, urine, and PN Zn measured monthly after AA changed from a standard to a pediatric product with varying dosages of cysteine.	Compare: Amount of Cr and Zn measured in 11 typical long-term pediatric PN solutions vs expected (prescribed) Outcome: Amount of Cr and Zn in these PN bags	To measure serum, urine, and PN Cr and Zn concentrations in pediatric patients receiving long-term PN Findings: In all cases the dose of Cr (and in some Zn) provided to patients significantly exceeded prescribed dose, likely due to contaminants in PN components	At baseline, the prescribed parenteral infant/child Cr dosage averaged 0.18 μg/kg per day but amount delivered was 0.41. Prescribed and delivered Zn doses were 177 and 238 μg/kg per day, respectively. Serum and urine Cr concentrations were abnormally high in infants and children receiving PN supplementation with normal doses of TEs. An escalating dose of cysteine in children tended to increase serum and urine Zn concentrations.	

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Table 14. (continued)

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Pluhator-Murton, 1999[90,91]	In vitro 8 PN component solutions (NaCl, KCl, Travasol 10%, MTE-6, CaGlu, MVI adult, Mg sulfate, sterile water) from 3 separate lots, tested for multiple TE contaminants using multielement technology of ICP-MS. Component amounts calculated by proportion needed to make a typical 1-L PN solution.	Comparison: Amount of trace element contaminants measured vs expected levels (as labeled) in PN solutions	To determine the extent that TEs are present as contaminants and as expected constituents (as labeled) in components used to prepare PN solutions and to examine degree of interlot variation for each component Outcome: Amount of PN trace contamination Finding: Higher than expected	TE contaminants present in all components expected to be free of TEs. Of 66 elements scanned, ICP-MS found 12 TE contaminants in the PN solutions: Zn, Cu, Mn, Cr, Se, B, Al, Ti, Ba, V, As and Sr. The multi-TE component contained TEs both above or below labeled and was contaminated with Al and B. Significant intralot variation of TE contamination present in components from same manufacturer and between them. Clinical relevance examined with calculation of amount of expected contamination TE in 2 L of PN based on results. This showed a greater amount of all TEs than expected with 8 of the 12 TE contaminants (Zn, Cu, Mn, Cr, Se, Al, Ba, and V) present in amounts greater than average daily oral intake levels.	Precautions used to prevent extraneous TE contamination. NIST quality control followed Results reported as means of TE/L of PN solution Cr contamination of 2 L of PN approximately 15 µg/d (mainly from 70% dextrose); final dose 30–60 times higher than estimated requirement Indicated PN solution components may deliver significant amounts of TEs over physiologic requirements
Pluhator-Murton,1999[90,91]	In vitro 4 typical home PN solutions compounded (1 lot of each). Zn, Cu, Mn, Se only added. PN solution "delivery" collected in polypropylene bottles Effects of delivery apparatus, time, temperature, freezing analyzed. Four time/temperature combinations reported	Comparison: Amount of TEs (includes contamination) in PN when compounded vs post storage Outcome: Amount of TEs measured Finding: Decreased by storage duration and higher temperature	To determine stability of TEs relative to time and temperature conditions in a typical adult PN solution stored in a typical home environment	Storage duration and temperature significantly decreased Zn, Cu, Mn, that were formulated into PN. B, Al, V, Ti, Ba, Sr, and Co appeared as contaminants during storage. Boron, Al, V, and Ti contamination decreased with higher temperatures and longer storage duration.	Precautions against contamination from compounding equipment taken. NIST and other quality control stability data reported. Authors concluded that longer storage time and higher storage temperature progressively decreased deliverable amounts of TEs formulated into PN and also of the TEs not formulated in the PN but that appeared as contaminants.
Popinska 1999[106]	In vitro Al concentration of small-volume parenteral solutions (AAs, IVFE, and special solutions of AA, glucose, electrolytes, and TEs [standard neonate solutions]) were analyzed via graphite furnace atomic absorption spectrometry	Compare: Al content of standard neonate solutions vs expected (safety limits) Outcome: Al measured in standard neonate PN solutions	To measure the Al concentration in small-volume parenteral solutions as described in methods Finding: Al intake exceeds safety limits. Ca gluconate, vitamins, TEs, and IVFE contained highest amount	The Al intake from PN was 6.6–10.8 µg/kg per day, which exceeds the safety limit of 2 µg/kg per day Phosphates, Ca gluconate, lipid-soluble vitamins, TEs (1 of the 2 manufacturers tested), and 1 of the 20% IVFEs contained the highest amount of Al	Needles with Al hubs also tested Internal/external quality control measures used
Hak, 1998[100]	In vitro Solutions of AAs, cysteine, dextrose, electrolytes, minerals, vitamins, multiple TEs, and individual TE from varied manufacturers, lots, and expiration dates used for a PN formula for <10 kg infant The solutions were analyzed for Cr and Zn by flame AAS	Compare: Amounts of Cr and Zn measured in common components of a typical neonate PN solution vs expected (labeled amounts) Outcome: Amount of Cr and Zn as measured	To measure Cr and Zn in PN solution components, to determine if there is a relationship between amount of contaminant and the storage time and container size, and to calculate the amount of contaminant Cr and Zn that typically would be provided to an infant by a PN solution Finding: Contamination may result in delivery of Cr and Zn	In all AAs, Cr was less than the limit of detection, and Zn ranged from 0.06 to 4.97 mg/L. In the L-cysteine hydrochloride, Cr was measurable in only 2 lots (0.11, 0.23) and Zn was measurable in all lots (32–86 mg/L). Cr and Zn concentrations were highest in the PTE-4 and the multi-trace products. There was no relationship between the expiration date and	Products passed expiration date also included Authors conclude that contamination may be sufficient to result in administration of Zn and Cr in amounts exceeding current recommendations

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Table 14. (continued)

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
	The amounts of Cr and Zn that would be provided as contaminants were calculated for each product		exceeding current recommendations	Cr and Zn content. In 4 lots of MTEs, Cr was 92%–104% and Zn was 100%–113.5% of the labeled amount. The infant PN solution compounded from assayed components would provide up to an additional 0.7 mg of Cr per kg and 200 μg of Zn per kg.	
Pluhator-Murton, 1996[93]	In vitro 4 experimental groups: SWFI from manufacturer, PN bags manually filled with SWFI, PN bags autofilled with SWFI, and SWFI manually added directly to sample vials, bypassing PN bag. Bags stored for 16 h at 4°C, then analyzed for 66 TEs by ICP-MS	Comparison: TEs as compounded vs measured Outcome: Measured TEs in compounded PN bags	To study the extent and sources of TE contamination during simulated manual and automated compounding of PN solutions Finding: Minimal increase in TE contamination due to compounding process	3 TEs present as contaminants in each experimental group (Zn, B, Al). Very low background amounts of Zn, B, Al found to contaminate SWFI as received from manufacturer. Manual or automatic compounding of PN did not contribute additional B or Al; Zn found at 35.4 μg/L. 12.4 from compounding equipment, 9.1 from PN bag, 13.9 from SWFI.	Zn higher than background level but not nearly enough to satisfy physiological requirements Concluded that simulated compounding of PN (manual or automatic) provides minimal TE contamination
Leung,1995[95]	OBS Serum TEs including Se, Cr, and Al were monitored over 14 months. Al content of PN nutrients and additives was also measured. After finding that the Ca gluconate contained significant Al contamination, it was removed and CaCl was added.	PN-dependent 74-year-old patient with mesenteric fibrosis/small bowel fistula on PN in hospital and home Comparison: Amount of Al and Cr in PN vs expected (minimal/none)	To describe trace metal changes in a 74-year-old patient Outcome: Degree of TE contamination Finding: Increased Al, Cr	Serum Cr levels were 21 times upper reference range; serum Se was <0.5 the lower reference range. Serum Al was 2 times the upper reference range. PN Al of all components measured with Ca gluconate found to contain most of the contaminating Al in the solution. The major source of Cr was crystalline amino acids. Cu, Se, Zn were not significant. Replacing Ca gluconate with CaCl reduced the Al content of final PN solution by 34% (still unsafe range). Serum Al levels eventually fell to nearly the upper end of reference range.	Patient with normal renal function Patient with low Se levels—authors propose that Se may be used by patient to buffer the additional Al in plasma due to Al contamination Concluded Al contamination must be addressed and more research is needed on clinical effects of Cr contamination and toxicity
Moukarezel, 1992[101]	OBS 15 children on home PN for mean 9.5 y were studied for GFR, Cr intake, serum Cr concentration. Cr supplementation was stopped and children reassessed after 1 y	Home PN patients; Compare: Amounts of Cr delivered and serum Cr before and after stopping Cr supplementation in pediatric patients receiving PN home vs non-PN controls	To assess Cr intake, serum Cr concentrations, and renal function in 15 children receiving PN, and compare outcomes with the daily recommended intake Outcome: Amount of Cr measured in PN, serum Cr before and after stopping Cr supplementation in PNs	Contaminating Cr concentrations in PN 1.0–1.8 μg/L, IVFE 0.9 μg/L. Mean serum Cr concentration fell but was significantly higher than in controls after supplementation stopped; no change in GFR, no patients with signs of Cr deficiency Finding: Even though children received less than recommended Cr intake, serum levels were 20 times higher than non-PN controls	Authors concluded: Although patients received less than recommended Cr intake during supplementation, high Cr levels suggested excessive intake and recommend that parenteral Cr intake for children should be lowered
Ito, 1990[102]	In vitro A variety of commercially produced solutions and additives commonly used in PN formulations analyzed for Cr. Total Cr to be administered per day was estimated	Compare: Amount of Cr measured in common components of typical PN solutions, then estimated total Cr likely to be given daily vs expected (reference range)	To measure the amount of Cr that would unintentionally be administered in PN Finding: Contaminating Cr approaches or is equal to minimum dose of reference range by AMA expert panel (10–15 μg/d)	Storage of solutions in plastic bags for 14 d did not affect results. The amounts ranged from 2.4–8.1 μg/d for high glucose formula to 2.6–10.5 μg/d for a high IVFE formula. AA solutions, especially when containing	Major contamination. Sources: AAs, phosphate salts, and IVFEs used in large quantity (86% of Cr contamination). Variations lot to lot. No reports of toxicity in literature.

(continued)

Table 14. (continued)

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
	by summing the Cr in appropriate volumes of each PN component and by analyzing complete PN solutions. Measurements were done with flameless AAS.	Outcome: Amount of measured Cr and estimated daily dose		phosphate or IVFE, accounted for 85%–90% of the Cr found.	Authors recommend Cr supplementation be continued until precise balance data on long-term PN patients are available.
Berner, 1989[96]	In vitro Concentrations of the selected ultratrace elements were measured in each component of the PN solution prior to mixing from different lots; typical daily intake calculated. Ultratrace amounts in mixed solutions analyzed after storage for 4 wk at 4°C; PN solutions were chemically "digested" prior to analysis (HNO_3, sandbath at 160°C).	Comparison: Amount of ultratrace elements vs amount absorbed in normal subjects Outcome: Amount of contamination from ultratrace in different PN components Finding: Increased Mo, Ni, V, and Cd	To determine the intake of selected ultratrace elements (Al, B, Ni, V, Al, and Cd) from a standard PN solution and compare it with the amount reported to be absorbed from food in normal subjects. B is much lower while Al is much higher (20 times).	The contamination from different lots and manufacturers varied markedly. Daily intakes of Mo, Ni, V, and Cd from contamination were comparable to amounts reported to be absorbed through the GI tract in normal subjects. Significant contribution for some of the elements came from AA and dextrose solutions because of daily volume needed for clinical use. Significant contributions from the electrolyte solutions (highest in Ca gluconate, K, phosphate, and Mg sulfate) and SWFI from contamination seen.	SWFI did not contain measureable amounts of ultratrace elements Ultratrace measurements determined with ICAP emission spectrometry Standard PN mixed with stock solutions of ultrapure metals and deionized water Due to the age of this study, the PN solutions contained more dextrose than currently typical
Koo, 1986[107]	In vitro Al concentration measured in 136 samples from commercially available components used in compounding infant PN solutions. Al measured by electrothermal AAS.	Compare: Amount of Al in common components of neonate PN solutions vs expected (safety limits). Outcome: Amount of Al measured in components of neonate solutions	To determine extent of Al contamination of frequently used components of PN solutions used for infants and components with high Al; explore alternatives with low Al content Finding: High amounts found in Ca and phosphate salts, MVI, albumin. Lowest in AAs, SWFI, dextrose water, chloride salts of sodium, potassium, Ca, Cu, Cr, sodium, phosphate, Mg sulfate, Zn, vitamin B_{12}, vitamin K, 1 MVI prep, soybean oil, and heparinized saline.	Al content varied widely based on manufacturer but similar among lots from same manufacturer. Sources with highest amount of Al included most Ca and phosphate-containing salts, 1 MVI prep, folic acid, ascorbic acid, and 25% albumin. Intermediate amounts found in Na lactate, K phosphate, Zn, chromium chloride, MTE, and 5% plasma protein. The low group included AAs, SWFI, dextrose water, chloride salts of sodium, potassium, Ca, Cu, Cr, sodium, phosphate, Mg sulfate, Zn, vitamin B_{12}, vitamin K, 1 MVI prep, soybean oil, and heparinized saline. Ca gluconate contributed >80% of total Al load.	
Kurkus, 1984[92]	In vitro 19 different sterile, large-volume PN solutions and various nutrient additives sampled for presence of Mn using flameless AAS. Analysis of 8 actual PN solutions was also done.	Compare: Amount of Mn measured in common PN components and 8 PN compounded solutions vs expected	To analyze a variety of commercially produced solutions and additives commonly used to compound PN for Mn Outcome: Amount of Mn as measured Finding: Many components of PN contaminated with Mn; however, amount is small (<1/7 of lower limit: 0.15–0.8 mg)	The amount Mn varies between manufacturers and among lots. It was present in very small amounts, with AAs supplying the major proportion in PN formulas. Some additives were high: K phosphate with 280 µg/L, Mg sulfate with 225 µg/L and Berocca C with 245 µg/L, but actual contribution to PN was 3.3 µg. IVFE contributed 0.5 and 3 µg/L, respectively.	PN solutions were in 1- and 2-L PVC Abbott bags sampled several days after preparation. Mn is very stable, as no decrease occurred in PN solution over 14 d. These authors concluded that contamination occurred from the manufacturing process or raw materials (including water source), not stoppers. Use of MTE solutions may not provide needed flexibility to regulate Mn intake or that of other TEs.

(continued)

Table 14. (continued)

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Smith, 1980[108]	In vitro Se levels in solutions used to compound PN were measured using a modification of the fluorometric method of Watkinson. Records of 4 patients on different PN formulas were pulled (representing >100 bottles of PN solution) and reviewed; average Se intake calculated.	Compare: Amount of Se measured in common PNs with average Se intake calculated vs expected	To analyze a variety of solutions used to make PN for selenium	Major source of Se in solutions was dextrose and did not vary with the concentration (20%, 50%, 70% from different manufacturers). In a PN formulation of 3 L, 233 mcg of Se was provided; at least 80% of total Se would be supplied by dextrose and most of remainder by AA. Vitamin and Ca gluconate contain high concentration per liter, but a relatively small volume is added to PN. Generally small variations in lots found.	Double checked by independent laboratory Per authors, source of contamination likely not dextrose, but manufacturing process
Jetton, 1976[94]	In vitro Various IV solutions chosen at random by lot number from hospital pharmacy. 2 bottles of PN were assayed. 1 aliquot removed and underwent direct measurement of TEs (Mg, Ca, Zn, and Cu) and measured by atomic absorption. Another concentrated 10× and used for analysis if direct measurement nondetectable. Bottles, tubing, and stoppers were rinsed in deionized water and soaked in TE-free nitric acid, which was then analyzed for Mg, Zn, Ca, and Cu.	Comparison: Amount of TEs measured in typical PN vs expected (0) Outcome: Amount of TEs measured Finding: Increased Zn, Mn	To determine the TE content of various IV solutions and to then seek out the source of contamination	Variable levels of Zn, Ca, and Mg found in solutions. In effort to identify source, tubing and stopper analysis showed rubber stoppers to be greatest source of TE contamination in solutions.	Amount of Zn in typical PN + 12 mg found as contamination would total 22 mg of Zn per day. Mn calculated in same way by authors would result in excessive Mn administration. Variability of TEs found and thus delivered to patient is of concern. Authors urge extreme caution in adding TEs to PN. Glass bottles with rubber stoppers have been largely replaced by plastic IV bags

AA, amino acid; AAS, atomic absorption spectrometry; Al, aluminum; AMA, American Medical Association; As, arsenic; B, boron; Ba, barium; Ca, calcium; CaCl, calcium chloride; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; FDA, U.S. Food and Drug Administration; Fe, iron; Ge, germanium; GFR, glomerular filtration rate; GI, gastrointestinal; ICAP, inductively coupled argon plasma; ICP-MS, inductively coupled plasma-mass spectrometry; IV, intravenous; IVFE, intravenous fat emulsion; K, potassium; Mg, magnesium; Mn, manganese; Mo, molybdenum; MTE, multi–trace element; MVI, multivitamin for injection; Na, sodium; Ni, nickel; NIST, National Institute for Standards and Technology; OBS, observational study; Pb, lead; Phos, phosphorus; PN, parenteral nutrition; Se, selenium; Sn, tin; Sr, strontium; SWFI, sterile water for infusion; TE, trace elements; Ti, titanium; V, vanadium; Zn, zinc.

as contaminants in a number of PN components.[90,91,95,99-102] This may necessitate the use of individual rather than fixed-dose multi–trace element products to allow dosing flexibility for patient PN regimens when contaminants are of concern. Further research is recommended on micronutrient contamination of PN.

Question 9. Is it safe to use the PN admixture as a vehicle for non-nutrient medication delivery?

Recommendation: We recommend that non-nutrient medication be included in PN admixtures *only* when supported by (1) pharmaceutical data describing physicochemical compatibility and stability of (a) the additive medication and (b) the final preparation under conditions of typical use, and (2) clinical data confirming the expected therapeutic actions of the medication. Extrapolation beyond the parameter limits (eg, products, concentrations) of the given data is discouraged.

GRADE: Strong (Table 15)

Rationale: Taking into account all of the contents, the stability and compatibility of PN admixtures are pharmaceutically complex in the absence of drug additives.[109,110] Given this complexity, caution is required before introducing substances (including medication) not known to be compatible and stable with PN and without knowing the consequence to the integrity of the PN preparation. The inclusion of non-nutrient medication with PN admixtures has not generally been.[2] However, there are potential advantages to including medication in the PN admixture (eg, consolidating drug dosing and volume, reducing violations of the vascular access device). Any medications considered should be limited to IV drugs with stable regimens, which are therapeutically effective by continuous infusion and do not require dose titration.[111]

Nearly 75% of respondents in a national survey allow non-nutrient medication to be added to PN admixtures.[112] Most frequently included are insulin, heparin, and the histamine type-2 receptor antagonists. Much less commonly included are albumin, digoxin, dopamine, erythropoietin, furosemide, hydrocortisone, methylprednisolone, metoclopramide, octreotide, and ondansetron. While many of these medications have been evaluated, the study conditions and data reported may not always support their inclusion. Some medication (eg, albumin) is not recommended for inclusion in PN.[113] Other drugs (eg, heparin) are not recommended for 3-in-1 PN admixtures because of influences on the integrity of the emulsion.[114-116] Therefore, including non-nutrient medication in PN admixtures is risky in the absence of appropriate evidence indicating compatibility and stability.[111]

Specific criteria for evaluating compatibility and stability studies of medication in PN are well recognized and should be met.[111,117] Any potential for incompatibility or instability as a result of physical-chemical interaction poses a safety concern. Studies should provide a complete description of the PN and the medication, use drug stability-indicating assays, obtain multiple sample points over at least 12–24 hours in replicate, describe physicochemical properties, and simulate conditions of actual use.[111,117] Physical compatibility is not necessarily indicative of chemical compatibility.[118] Furthermore, physical compatibility and chemical stability alone are not sufficient to include a medication in a PN admixture. Pharmacologic or therapeutic efficacy must be maintained or improved, without any increase in adverse reactions, when administered as part of the PN regimen and requires a clinical study. The continuous IV administration of drug via PN admixtures may be more effective at maintaining therapeutic drug concentrations compared with intermittent dosing. This was demonstrated in a clinical study for the histamine type-2 receptor antagonist cimetidine.[119] Only 29% of serum values were subtherapeutic when administered continuously via PN compared with 70% when the drug was administered every 6 or 8 hours.[119] In this case a clinical study was possible because of a previous compatibility/stability study.[119,120] In contrast, few studies are of adequate quality to support PN inclusion of non-nutrient medications in practice.

Most of the earlier studies contained serious flaws in both study design and results reporting. Primary among these was using visual rather than quantitative documentation of compatibility and stability.[111] Visual compatibility is not sufficient and eliminates many of the available publications.[118,120-123] The remaining studies suggest that only a few medications (eg, histamine type-2 receptor antagonists) may be included in PN admixtures with specifically defined contents. The PN formula composition will in part determine the availability of drug to the patient's circulation.[124] A number of studies using 3-in-1 PN admixtures were published prior to the USP criteria on emulsion stability.[125] Closer examination of the reported results may prove less acceptable if the percentage of fat particles >5 μm exceeds the 0.05% limit. A drug with in vitro compatibility and stability in a PN admixture would still need to be shown to be clinically effective in humans before it can be recommended.

Beyond compatibility and stability in the PN admixture is the compatibility of the medication with the administration system (PN container, administration set, and inline filter), which is seldom evaluated. In the patient with limited access, an alternative to including medication in the PN container is to consider administering via Y-site into the same line. The compatibility of coinfusion of medication via Y-site has also been studied in vitro for commonly used medication in adult, pediatric, and neonate patients.[126-129] The number of formulations tested and study conditions are usually limited. A systematic evaluation of 102 drugs revealed that 82 (80%) were physically compatible with four 2-in-1 PN admixtures.[126] A similar evaluation of 106 drugs revealed that 83 (78%) were physically compatible with nine 3-in-1 PN admixtures.[127] An evaluation of 25 medications revealed that 20 (80%) were considered compatible with a 3-in-1 PN admixture.[128] Only 5 drugs out of

Table 15. Evidence Summary, Question 9: Is It Safe to Use the PN Admixture as a Vehicle for Non-Nutrient Medication Delivery?

Author, Year, Reference No.	Study Design	Non-Nutrient Medication(s)	Study Objective	Results	Comments
Gellis, 2007[130]	In vivo	Methylprednisolone	To study the pharmacokinetic and dynamic effect of methylprednisolone administered via PN admixture	At a concentration of 100 mg/L, there were no differences in methylprednisolone pharmacokinetics between PN formulations; the drug was bioavailable with serum concentrations exceeding EC_{50} values	One 2-in-1 and one 3-in-1 formulation Additives included electrolytes, multivitamins, and trace elements Rabbit model
Christianson, 2006[131]	In vitro	Insulin	To evaluate the availability of insulin from standard PN solutions	At 10 units/L, insulin recovery was much greater from PN solutions containing multivitamins/trace elements than those without ($P < 0.001$) at all time points evaluated; at 1 h into the infusion, there was already a difference in insulin availability (96% vs 4.5%, $P < 0.001$)	2-in-1 formulation Additives included electrolytes, but multivitamins and trace elements were only included in the first of 2 daily PN solutions Insulin Humulin-R Insulin determined by RIA method 24-h simulated infusions Glass container/PVC infusion set
Rusavy, 2004[132]	In vitro	Insulin	To assess the effect of carrier intravenous solutions (saline vs PN) on the biologic availability of insulin	At a concentration of 8 units/20 mL, insulin availability was nearly 5 times higher from the PN admixture than from the saline solution ($P < 0.001$); this difference was sustained at all time points studied	3-in-1 PN formulation Micronutrient additives included only trace elements Insulin Actrapid HM (Novo Nordisk) Insulin determined by RIA method 3.5-h simulated infusion PVC container/infusion set
Huynh-Delerme, 2002[133]	In vitro	Erythropoietin	To assess stability and biological activity of erythropoietin beta in a PN solution over 24 h	At a concentration of 1.3 units/mL in the PN solution, erythropoietin was stable; however, 23%–39% of the drug is lost on passage through the 0.2-µm filter; drug present in the samples remains bioactive	2-in-1 formulation Additives included electrolytes, multivitamins, and trace elements Erythropoietin determined by ELISA Bioactivity determined by cell culture
Gellis, 2001[134]	In vitro	Methylprednisolone (sodium succinate)	To study the stability of methylprednisolone in PN admixtures To study the influence of the drug on PN admixture stability	Methylprednisolone remains stable in both PN admixtures at 25, 62.5, and 125 mg/L for 7 d at 4°C and following 24 h at room temperature and lighting No significant influence of storage conditions or the drug on nutrient stability	One 2-in-1 and one 3-in-1 formulation Additives included electrolytes, multivitamins, and trace elements EVA containers Emulsion evaluated for particle-size distribution but data not provided Main nutrients assayed
Allwood, 1996[135]	In vitro	Cimetidine	To determine the extended stability of cimetidine in PN solutions of varying amino acid composition	Cimetidine remained stable in each of the PN solutions at 80 mg/L for 28 d at 5°C	Three 2-in-1 formulations varying only in amino acid product Additives included electrolytes and trace elements EVA containers

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Table 15. (continued)

Author, Year, Reference No.	Study Design	Non-Nutrient Medication(s)	Study Objective	Results	Comments
Hensrud, 1996[136]	In vitro	Heparin	To determine the activity of heparin added to PN and stored under conditions of use in home PN	At heparin concentrations of 3000–20,000 units/L, there was no significant change in heparin activity over 24 h and <10% change over 3–28 d when stored at 4°C	Four 2-in-1 formulations varying in heparin concentration Additives included electrolytes and trace elements without vitamins Used DEHP-free plastic Activity determined by antifactor Xa assay
Matsui, 1996[137]	RCT Patients with Crohn's disease and PN with 200 or 400 mg ranitidine daily	Ranitidine	To study the effects of 2 different doses of ranitidine administered continuously in PN solutions on gastric pH of patients with Crohn's disease requiring PN therapy, N = 11	Mean 24-h, daytime, and nighttime gastric pH was significantly higher ($P < 0.05$) during PN infusion containing ranitidine than PN without the drug; there was no significant difference between the 2 doses of ranitidine (both achieved serum concentrations well above the effective concentration range); neither dose was able to maintain gastric pH ≥3.5	Drug stability not evaluated Intragastric pH monitored continuously over 24 h period in the presence and in the absence of ranitidine
Kirkham, 1995[138]	In vitro	Ondansetron	To study the stability of ondansetron in a PN admixture	Ondansetron remained stable in the PN admixture at 30 mg/L for 48 h at room temperature and lighting; no visual evidence of physical incompatibility	3-in-1 formulation Additives included electrolytes, multivitamins, and trace elements Emulsion not evaluated
Ritchie, 1991[139]	In vitro	Octreotide	To study physical compatibility and chemical activity of octreotide in PN admixtures	Octreotide at a concentration of 450 µg/L was not uniformly stable at 12, 24, or 48 h at room temperature Emulsion integrity and fat particle size did not change appreciably	3-in-1 formulation Additives included electrolytes, multivitamins, and trace elements Both EVA and glass containers Octreotide assayed by RIA Emulsion evaluated for particle-size distribution
Driscoll, 1990[119]	RCT Patients 2-in-1 PN or 3-in-1 PN containing cimetidine 600, 900, or 1200 mg/d, or to intermittent cimetidine at 300 mg every 8 h or every 6 h	Cimetidine	To investigate the ability of continuous drug infusion via PN admixtures to achieve therapeutic serum concentrations in acutely ill patients compared with intermittent intravenous drug dosing, N = 27	Continuous infusion of cimetidine via PN admixtures maintains therapeutic serum concentrations more consistently than does intermittent administration; no differences noted between 2-in-1 and 3-in-1 PN	Drug stability not evaluated Gastric pH to evaluate efficacy not performed
Marcuard, 1990[124]	In vitro	Insulin	To evaluate insulin availability from PN admixtures compared with saline (0.9% NaCl)	At concentrations of 10, 25, and 50 units/L, insulin recovery remained at >90% from the PN admixtures (except for those using hepatamine ~87%)	Both 2-in-1 and 3-in-1 formulations varying in amino acid product Additives included electrolytes, multivitamins, and trace elements

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Table 15. (continued)

Author, Year, Reference No.	Study Design	Non-Nutrient Medication(s)	Study Objective	Results	Comments
				compared with 65% recovery from saline ($P < 0.001$); insulin binding to the injection port (1.5%–3.2%) exceeded that from the PN bag or tubing.	Insulin Humulin-R Insulin determined by ^{125}I-labeling 24-h simulated infusion EVA container
Williams, 1990[140]	In vitro	Ranitidine	To evaluate ranitidine stability in PN admixtures stored at room temperature or refrigerated, protected from or exposed to light To examine the effect on the stability of amino acids and the emulsion	Under all conditions tested, ranitidine remained stable at 37–45 and 74–91 mg/L for 24 h; all ranitidine in 2-in-1 PN admixtures remained stable for 48 h Emulsion integrity, fat particle size, and amino acid concentrations remained unchanged by ranitidine over 48 h.	Both 2-in-1 and 3-in-1 formulations (4.5%/22.7%/0% and 3.7%/18.5%/3.7% amino acid/dextrose/fat) Additives included electrolytes only EVA containers Emulsion evaluated for particle-size distribution
Bullock, 1989[141]	In vitro	Famotidine	To assess the stability of famotidine in PN solutions and the stability of amino acids in presence of the drug	Famotidine remained stable at 20 and 40 mg/L at 24 h, 48 h, and 7 d in all PN solutions at room temperature or refrigerated Amino acids were not affected in PN solutions containing 40 mg/L famotidine compared with controls	2-in-1 formulations varying in amino acid concentration (20 g/L, 42.5 g/L) Additives also included multivitamins, and trace elements EVA containers
Bullock, 1989[142]	In vitro	Famotidine	To determine the stability of famotidine in PN admixtures and the stability of the emulsion over 24 h at 4°C followed by 24 h at room temperature	Famotidine remained stable at 20 and 50 mg/L for the 48-h study period Emulsion integrity was unchanged over 48 h; mean particle radius did not exceed 480 nm (fat emulsion at baseline was 420 nm) and minimal change in percentage of particles >5 µm during the study	Two 3-in-1 formulations varying in amino acid concentration (21.25 or 42.5 g/L) and fat concentration (25 or 40 g/L) Additives included electrolytes, multivitamins, and trace elements EVA containers Emulsion evaluated for mean droplet radius, and particle size distribution including weight percentage as particles >5 µm
DiStefano, 1989[143]	In vitro	Famotidine	To assess the stability and compatibility of famotidine in a PN solution stored at 4°C for 35 d	Famotidine remained stable at 20 mg/L for the 35-d study period with no visual signs of incompatibility	A 2-in-1 formulation Additives included electrolytes and trace elements, but no vitamins PVC containers

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Table 15. (continued)

Author, Year, Reference No.	Study Design	Non-Nutrient Medication(s)	Study Objective	Results	Comments
Montoro, 1989[144]	In vitro	Famotidine	To determine the stability of famotidine in PN admixtures To evaluate the integrity of the emulsion over 72 h	Famotidine remained stable at 20 and 40 mg/L for the 72-h study performed at room temperature and lighting Emulsion integrity remained visually unchanged and exhibited no substantial changes in particle size distribution	Two 3-in-1 formulations varying in fat emulsion product (20% LCT or 20% MCT/LCT) Additives included electrolytes, multivitamins, and trace elements EVA containers Emulsion evaluated for particle size distribution
Walker, 1989[145]	In vitro	Famotidine	To investigate the stability of famotidine in PPN and PN solutions at both refrigerator and room temperature over 7 d	Famotidine remained stable at 16.7 and 33.3 mg/L in both PPN and PN solutions for the 7-d study at both 4°C and 23°C; visual change in color occurred with time in PPN and PN solutions stored at room temperature	Two 2-in-1 formulations varying only in dextrose concentration (42 or 210 g/L) Additives included electrolytes, multivitamins, and trace elements PVC containers (covered with UVL plastic bags at room temperature)
Cano, 1988[146]	In vitro	Ranitidine	To study the stability of ranitidine in PN admixture and the stability of the emulsion over 72 h	Ranitidine remained stable at 50 and 100 mg/L for only 12 h at room temperature Emulsion integrity was unchanged over 72 h	A 3-in-1 formulation Additives included electrolytes, multivitamins, and trace elements EVA containers Emulsion evaluated for particle size distribution
Pesko, 1988[147]	In vitro	Metoclopramide	To determine the physical compatibility and chemical stability of metoclopramide in PN solutions	Metoclopramide remained stable at 20 mg/L in both PN solutions for 48 h; at the 5-mg/L concentration, metoclopramide is only stable 24 h	Two 2-in-1 formulations varying only in the presence of electrolytes No other additives
Raupp, 1988[148]	In vitro	Heparin	What causes flocculation of fat emulsion when administered together with PN solutions administered to neonates?	Flocculation and creaming occurred when PN contained heparin and calcium, even at low doses	3-in-1 formulations with varying electrolytes and heparin
Underberg, 1988[149]	In vitro	Famotidine	To elucidate the stability of famotidine in commonly used PN formulations	Famotidine remained stable at 20 mg/L in various PN admixtures for up to 48 h refrigerated or at room temperature with daylight or in the dark	Both 2-in-1 and 3-in-1 formulations Additives not described
Baptista, 1985[121]	In vitro	Digoxin, dopamine, furosemide, isoproterenol, lidocaine, methyldopate, norepinephrine	To evaluate visual compatibility of medications in a typical PN admixture	Only methyldopate disrupted the PN emulsion based on visual findings at time 0, 1, and 4 h	A 3-in-1 formulation Additives included electrolytes, multivitamins, and trace elements Used a 1:1 dilution of PN and drug solution

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Table 15. (continued)

Author, Year, Reference No.	Study Design	Non-Nutrient Medication(s)	Study Objective	Results	Comments
Baptista, 1985[120]	In vitro	Cimetidine	To determine stability of cimetidine in PN admixture and any influence on emulsion stability	Cimetidine remained stable at 600, 1200, and 1800 mg in 1500 mL of PN admixture for 24 and 48 h at room temperature; emulsion stability at 24 h only	A 3-in-1 formulation Additives included electrolytes, multivitamins, and trace elements Emulsion evaluated for particle-size distribution
Bullock, 1985[150]	In vitro	Ranitidine	To assess stability of ranitidine in 2 PN solutions and the stability of amino acids in presence of the drug over 48 h	Ranitidine remained stable at 50 and 100 mg/L at 12 and 24 h in all PN solutions at room temperature Amino acids were not affected in PN solutions containing 100 mg/L ranitidine	2-in-1 formulations varying in amino acid concentration (2.125%, 4.25%) and presence of electrolytes Additives also included multivitamins, and trace elements PVC containers
Walker, 1985[151]	In vitro	Ranitidine	To evaluate the stability of ranitidine in a standard PN solution over 7 d	Ranitidine was stable at 100, 200, and 300 mg in 1200 mL of PN solution at 24 h; with 10% loss of drug by 48 h at room temperature	A 2-in-1 formulation Additives included electrolytes, multivitamins, and trace elements
Niemiec, 1983[152]	In vitro	Aminophylline	To assess compatibility and stability of aminophylline in several PN solutions under routine conditions	Aminophylline was stable at 0.25, 0.5, 1, and 1.5 mg/mL in PN solutions using Aminosyn (Hospira), FreAmine (B. Braun), and Travasol (Baxter) at 24 h at 4°C and 25°C	2-in-1 formulations Final amino acid concentrations from 1% to 4.25% were studied Additives included electrolytes, multivitamins, and trace elements
Tsallas, 1982[153]	In vitro	Cimetidine	To study the stability of cimetidine in PN solutions over 24 h at room temperature and 4°C	Cimetidine at 300 mg/L was found to be visually compatible initially and at 24 h whether stored at room temperature or refrigerated Cimetidine was stable in each of the solutions and conditions tested over 24 h	Four 2-in-1 formulations varying in micronutrient content (electrolytes, vitamins, trace elements) Additives included electrolytes in all PN solutions PVC containers
Moore, 1981[123]	OBS	Cimetidine	To observe serum drug levels in patients receiving cimetidine (900–1350 mg/24 h) via PN, N = 4	Continuous infusion of cimetidine via PN resulted in steady-state serum concentrations of 0.6–1.0 mg/L No precipitates noted and no apparent adverse consequence	Drug stability not evaluated Gastric pH to evaluate efficacy not performed
Rosenberg, 1980[154] and Yuhas, 1981[155]	In vitro	Cimetidine	To document the physicochemical stability of cimetidine in a number of parenteral solutions for 24, 48, 72, 168 h at room temperature	At 120 mg/100 mL and 500 mg/100 mL, cimetidine visually compatible and chemically stable with each intravenous fluid.	Evaluated dextrose solutions and amino acid solutions individually as well as admixed with or without micronutrients

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Table 15. (continued)

Author, Year, Reference No.	Study Design	Non-Nutrient Medication(s)	Study Objective	Results	Comments
Athanikar, 1979[122]	In vitro	Aminophylline, amphotericin, ampicillin, carbenicillin, cephalothin, cefazolin, clindamycin, cyclophosphamide, cytarabine, dopamine, erythromycin gluceptate, fluorouracil, furosemide, gentamicin, heparin, regular insulin, isoproterenol, kanamycoin, levarterenol, lidocaine, metaraminol, methicillin, methotrexate, methyldopate, methylprednisolone, oxacillin, penicillin G, phytonadione, tetracycline, tobramycin	Evaluate visual compatibility of 30 drug additives in a commonly used PN solution	No observed difference in particulate matter over time; ampicillin, kanamycin, and penicillin G each resulted in at least 1 sample with particles >10 μm All amphotericin samples contained fine yellow particles Negligible pH change over time	Amino acid/dextrose solutions without micronutrients Time 0 and 24 h only
Schuetz, 1978[118]	In vitro	Insulin, ampicillin, kanamycin, cephalothin, gentamicin	Generate specific compatibility data for common PN additives	Insulin visually compatible at concentrations up to 50 units/L Antibiotics visually incompatible by 8 h, with ampicillin showing precipitation by as early as 4 h	2-in-1 formulation Electrolyte and vitamin content varied Antibiotic instability increased with higher Ca and P concentration

EC_{50}, 50% effective concentration; ELISA, enzyme-linked immunosorbent assay; EVA, ethylene vinyl acetate; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; NaCl, sodium chloride; OBS, observational study, PN, parenteral nutrition; PPN, peripheral parenteral nutrition; PVC, polyvinyl chloride; RCT, randomized controlled trial; RIA, radioimmunoassay; UVL, ultraviolet light.

131 (4%) were found compatible with PN via Y-site without restrictions.[129]

Question 10. Should heparin be included in the PN admixture to reduce the risk of central vein thrombosis?

Recommendation: We suggest that heparin not be included in PN admixtures for reducing the risk of central vein thrombosis in adults.

GRADE: Weak (Tables 16 and 17)

Rationale: Central venous access–related complications include infection, catheter occlusion, and thromboembolism.[156] Although including unfractionated heparin in PN admixtures may influence infection[157-159] and catheter occlusion,[160,161] these are multifactorial complications. A prospective trial of IV heparin infusion in patients with a central venous catheter was able to reduce (but not eliminate) the risk of thrombus formation compared with patients receiving no heparin prophylaxis.[162] The main interest for including heparin in PN is to reduce thromboembolic complications while minimizing volume burden.[111] However, a systematic review of the available evidence describes no significant decrease in catheter-related thrombosis (relative risk 0.77, 0.11–5.48) when heparin is included in the PN of patients with central vein catheters.[163] Additionally there is a potential problem of including heparin in PN admixtures that include fat emulsion. The stability of the emulsion is compromised (flocculation and creaming) because of an interaction between heparin and calcium.[148,164] This destabilization will depend on proportions of amino acids and fat emulsion and multivitamins.[165] Because including this high-alert medication has risks of its own, alternatives to reduce thromboembolic complications can be considered (eg, catheter type, line placement, and line care). Polyurethane catheters are less thrombogenic than polyethylene catheters. Fibrin can accumulate on catheters within 24 hours, which serves as a site for accumulation of particulate matter including bacteria.

Table 16. Evidence Summary, Question 10: Should Heparin Be Included in the PN Admixture to Reduce the Risk of Central Vein Thrombosis?

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Macoviak, 1984[166]	RCT Unfractionated heparin (1 unit/mL) vs no heparin	Adult males of VA surgical service, N = 37	What is the prophylactic value of low-dose heparin in PN to prevent venous thrombosis?	Subclavian thrombosis at 2 wk = 2/17 (11.8%) vs 1/20 (5%) (NS); at 4 wk = 4/17 (23.5%) vs 1/20 (5%) (NS)	Venograms PVC catheters Only 2-in-1 PN and IVFE through catheter; no other drug or blood products
Imperial, 1983[167]	Retrospective record review Group 1 = 1000 units/L, group 2 = 6000 units/d, group 3 = little or no heparin	All adult patients receiving PN from January 1976 through December 1980 by sequential groups: group 1 (n = 129), group 2 (n = 858), group 3 (n = 23)	To describe experience with addition of heparin to PN solutions for central vein thrombosis prophylaxis	Central vein thrombosis in group 1, 7/129 (5.4%); in group 2, 10/858 (1.2%); and in group 3, 4/23 (17%)	Venogram, history and physical, and/or at autopsy PVC catheters in group 1 (January 1976 to June 1977) and group 2 (July 1977 to December 1980) Silastic catheters for group 3 (July 1977 to December 1980) receiving cycled PN at home
Fabri, 1982[168]	RCT Unfractionated heparin (3000 units/L of PN) vs no heparin	Adult hospitalized patients, N = 46	What is the incidence of central vein thrombosis, and what is the effectiveness of heparin in preventing this?	Thrombosis = 2/24 (8.3%) vs 7/22 (31.8%) ($P < 0.05$)	Radionuclide venograms of both upper extremities at baseline and every 2 wk PVC catheters No difference in anticoagulant effect

IVFE, intravenous fat emulsion; NS, not significant; PN, parenteral nutrition; PVC, polyvinyl chloride; RCT, randomized control trial; VA, Veterans' Administration.

Table 17. GRADE Table, Question 10: Should Heparin Be Included in the PN Admixture to Reduce the Risk of Central Vein Thrombosis?

Comparison	Outcome	Quantity, Type Evidence, Reference No.	Finding	GRADE	Overall Evidence GRADE
Heparin vs no heparin	Central vein thrombosis	2 RCT[166,168] 1 OBS[167]	At 3000 units/L favors heparin in PN, but at 1000 units/L does not	Low	Low

OBS, observational study; PN, parenteral nutrition; RCT, randomized control trial.

Question 11. What methods of repackaging IVFE into smaller patient-specific volumes are safe?

Recommendation: We recommend against the repackaging of IVFE into syringes for administration to patients. We suggest that other methodologies for repackaged IVFE, such as drawn-down IVFE units, are preferable.

GRADE: Strong (Table 18)

Rationale: Repackaging IVFE into smaller patient-specific volumes is a common practice in institutions that care for neonates and infants. The primary reasons for repackaging are to minimize cost and waste of IVFE, to decrease risk of inadvertent IVFE overdose, and to allow for IVFE infusion via syringe pump technology. IVFE supports the growth of bacteria and fungi,[169-175] and microorganisms have been identified in IVFE after completion of infusion to patients.[176-179]

Systemic infection in neonates has been linked to multiple bedside caregivers repeatedly withdrawing IVFE doses from a single IVFE unit.[180-182] In addition, administration errors with IVFE including overdose have been documented in neonates.[183-186] For all of these reasons, institutions should develop IVFE administration guidelines that decrease the risk of microbial contamination while also preventing serious medication errors. With respect to IVFE infusion times, the American Academy of Pediatrics recommends continuous infusion of IVFE of up to 3 g/kg per day to promote optimal IVFE clearance in neonates and infants.[187] Providing IVFE as part of a TNA offers protection from microbial contamination[20-23] and allows for a 24-hour infusion time; however, TNAs are not recommended for use in neonates and infants due to concerns about stability and calcium and phosphate solubility.

While there are overwhelming data that IVFE is an excellent growth source for bacteria and fungi, only a few studies have evaluated microbial contamination of different methods of IVFE delivery under actual use conditions.[177-179,188] The methodologies for IVFE delivery that have been evaluated include separate infusion direct from the manufacturer's container, repackaged into a syringe, a drawn-down IVFE unit (ie, original manufacturer container with some of the volume purged aseptically), and repackaged bags with the use of an automated compounding device (ACD).

IVFE samples taken directly from manufacturers' containers and stored for up to 24 hours at room temperature or up to 5 days under refrigerated conditions have not grown bacteria or fungi.[188] Likewise, no growth has been seen after 24-hour infusion of IVFE direct from the manufacturer's container to pediatric patients.[179] Similarly, a single in vitro study has documented no contamination with drawn-down IVFE units when infused over 24 hours to pediatric patients.[179] In comparison, a 3.3% contamination rate has been reported for IVFE repackaged in syringes and infused over 12 hours,[179] while rates of 2.3%–6.6% have been reported for repackaged syringes infused over 19 hours or more.[177,178] A 7.9% contamination rate was reported from samples taken from IVFE bags repackaged by an ACD, and the positive cultures occurred in samples taken immediately after compounding, after 12 and 24 hours of storage at room temperature, and after storage for 5 days under refrigerated conditions.[188] All of these studies are limited by small sample size.

We recommend that further research determine the safest method of delivering repackaged IVFE to patients.

Question 12. What beyond-use date should be used for (a) IVFE dispensed for separate infusion in the original container and (b) repackaged IVFE.

Recommendation:

a. We recommend that the beyond-use date (BUD) for unspiked IVFE in the original container should be based on the manufacturer's provided information. The BUD for IVFE in the original container spiked for infusion should be 12–24 hours.
b. Although repackaged IVFE is not recommended, when used, the BUD for IVFE transferred from the original container to another container for infusion separately from a 2-in-1 PN solution should be 12 hours.

GRADE: Strong (Table 20)

Rationale: BUD is the date or time after which a compounded sterile preparation (CSP) shall not be stored or transported.[64] In general, the BUD is the point in time after which a CSP cannot be administered and is determined from the date and time the preparation is compounded. Considerations for determining BUD include stability, sterility, and risk level as determined by the USP Chapter <797>.[64] A CSP is defined as a dosage unit with any of the following characteristics: preparations prepared according to manufacturer's labeled instructions; preparations containing nonsterile ingredients or employing nonsterile components and devices that must be sterilized before administration; biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that possess either of the above 2 characteristics and which include, but are not limited to, baths and soaks for live organs and tissues, implants, inhalations, injections, powder for injection, irrigations, metered sprays, and ophthalmic and otic preparations.[64] Commercially available IVFEs in the United States are preservative-free, oil-in-water emulsions consisting of soybean oil, egg phosphatide, and glycerin with an adjusted pH range of approximately 6–9. IVFE is particularly susceptible to contamination or instability because of these unique formulation characteristics.[60,68,176-179,188-196] Several factors contribute to risk of negative clinical outcomes due to compromised IVFE sterility or stability including effect of the container material, length of infusion, length of time between infusion set change, effect of infusion from source container such as infusion from the original container, infusion as an IVFE admixture, and infusion of IVFE transferred to a secondary container.[60,68,176-179,188,194-196] The BUD for unspiked IVFE in original packaging is dictated by the manufacturer's expiration date (Table 19). The BUD for other product-specific conditions is defined by the manufacturer. The BUD for IVFE spiked for use for compounding TNA is defined by USP Chapter <797>. The BUD for spiked bulk IVFE approved only for compounding TNA is dictated by USP Chapter <797> standards or more conservative time if indicated by the manufacturer. IVFE combined with a PN solution or TNA is a moderate-level risk preparation. USP defines BUD for moderate-level risk CSP as 30 hours at room temperature and 9 days refrigerated.[64] IVFE transferred from the original container to a secondary container is defined by USP as a low-level risk CSP.[64] USP defines BUD for low-level risk CSP as 48 hours at room temperature and 14 days refrigerated. However, experimental and clinical data suggest a shorter BUD may be indicated for IVFE transferred from the original container because of higher contamination and stability risks.

Table 18. Evidence Summary, Question 11: What Methods of Repackaging IVFE Into Smaller Patient-Specific Volumes Are Safe?

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Ybarra, 2011[188]	In vitro	IVFE repackaged into smaller EVA bags with an ACD in an ISO class 5 environment (n = 152). The ACD programmed to pump 50 mL (n = 76) and 75 mL (n = 76) IVFE bags. 100 mL IVFE units direct from manufacturer's container (n = 40) served as controls IVFE bags were immediately transferred for filtration and plating (n = 38 repackaged IVFE and n = 10 controls) or were stored for 12 h at room temperature (n = 38 repackaged IVFE and n = 10 controls), 24 h at room temperature (n = 38 repackaged IVFE and n = 10 controls), or 120 h refrigerated (n = 38 repackaged IVFE and n = 10 controls) Sterility conducted by filtering samples with a 0.8-µm filter by vacuum filtration in a class II biological safety cabinet and then plated for growth on Tryptic soy agar with 5% sheep blood. Filters assessed for growth at 24 and 48 h	Evaluate the sterility and feasibility of using an ACD to prepare unit doses of IVFE	Microbial growth occurred in 12 of the 152 repackaged IVFE samples (7.9%) and none of the 40 controls. Samples grew gram-positive cocci (n = 5), gram-positive rods (n = 5), and yeast (n = 2). Positive samples grew from the bags cultured immediately (n = 2), bags stored for 12 and 24 h (n = 8), and bags refrigerated for 120 h (n = 2).	Small sample size Numbers of positive cultures in bags stored for 12 and 24 h are not reported separately
Crill, 2010[179]	In vitro	Method 1: IVFE infused over 24 h at patient bedside (n = 60). Samples collected at end of infusion and refrigerated overnight prior to sample collection and sending to microbiology laboratory. Method 2: IVFE repackaged into syringes in the ISO class 5 hood and infused at patient bedside for 12 h (n = 90). Most samples (n = 75) collected at end of infusion and delivered immediately to microbiology laboratory; some samples (n = 15) collected at end of infusion and refrigerated overnight prior to delivery to microbiology laboratory. Method 3: Drawn-down IVFE units prepared in the ISO class 5 hood located within an ISO class 7 cleanroom. Unit volume drawn down by pumping excess volume into a collection bag, which was discarded. Direct from manufacturer container with the decreased volume infused at patient bedside for 24 h (n = 60). Samples collected at end of infusion and refrigerated overnight prior to sample collection and sending to microbiology laboratory. All IVFE samples cultured in microbiology laboratory and incubated for 5 d using BacTAlert (Biomérieux) and Bactec (BD systems), then further subcultured on blood agar plate with olive oil for an additional 2 d.	Evaluate microbial contamination associated with different methods of IVFE preparation and delivery for neonates	Method 1: no growth at 7 d (n = 60) Method 2: 3 out of 90 samples (3.3%) with bacterial growth (2 with coagulase-negative *Staphylococcus* and 1 with both *Klebsiella oxytoca* and *Citrobacter freundii*). Two of these samples were sent immediately to microbiology laboratory while 1 was refrigerated overnight prior to sending to microbiology laboratory. Method 3: no growth at 7 d (n = 60) No significant difference in the number of contaminated IVFE samples among the 3 methods of IVFE preparation and delivery ($P = 0.13$)	Small sample size Inconsistency between methods with respect to refrigeration prior to sending for culture

(continued)

Table 18. (continued)

Author, Year, Reference No.	Study Design	Population, Setting, N	Study Objective	Results	Comments
Reiter, 2004[178]	In vitro	IVFE repackaged into syringes and infused at patient (newborn infants) bedside over 19–23 h with 24 h IV administration set replacement (n = 90). Samples (1–3 mL) were aspirated prior to the IV tubing change from the syringe and IV tubing via the catheter connection site proximal to the patient. All IVFE samples cultured using Bactec (BD System). Culture bottles were inoculated at bedside and delivered to the microbiology laboratory.	Evaluate the effect of a 24-h tubing set replacement policy on the contamination rate of repackaged IVFE	Two samples excluded as they were from a single patient with untreated *Staphylococcus aureus* conjunctivitis that had disseminated to blood and urine 2 out of 88 samples (2.27%) grew coagulase-negative *Staphylococcus*. Both of these samples were taken from the same patient on consecutive days.	Small sample size Samples withdrawn from catheter connection site, so samples contained a mix of IVFE from tubing and from syringe
Reiter, 2002[177]	In vitro	Group 1: syringes (n = 30) containing 5 mL of IVFE sent to microbiology laboratory immediately after repackaging under sterile conditions in the pharmacy. Samples cultured at 0 h (n = 30) and 24 h (n = 30). Group 2: 3–5 mL IVFE remaining in syringes after 20 h infusion via syringe pump at patient (NICU) bedside (n = 30). Samples cultured at end of 20 h infusion (generally 30–35 h after syringe preparation in the pharmacy). All IVFE samples cultured for aerobic and anaerobic bacteria in microbiology laboratory using direct inoculation into broth as well as cultured on agar plates. Samples cultured by using 3 media (MacConkey agar, blood agar, thioglycolate broth).	Determine the sterility of 20% IVFE after transfer to plastic syringes for use with a syringe pump	All 90 samples (60 from group 1 and 30 from group 2) were negative for bacterial growth at 24 and 48 h 3 out of 90 samples (3.3%) grew gram-positive rods at 7 d. The positive samples were as follows: Group 1: 1/60 samples (1.7%) Group 2: 2/30 samples (6.6%)	Small sample size

ACD, automated compounding device; EVA, ethylene vinyl acetate; ISO, International Organization for Standardization; IV, intravenous; IVFE, intravenous fat emulsion; NICU, neonatal intensive care unit.

Table 19. BUD Considerations for IVFE in the Original Container.[2-7]

IVFE Product	BUD
Intralipid 20% and 30% bulk (Fresenius Kabi; bag)	Once the closure is penetrated, the contents should be dispensed as soon as possible; the transfer of contents to suitable PN admixture containers must be completed within 4 h of closure penetration. The bag should be stored below 25°C (77°F) after the closure has been entered.
Liposyn III 30% bulk (Hospira; glass container)	Maximum time of 4 h from transfer set pin or implement insertion is permitted to complete transfer operations (ie, discard container no later than 4 h after initial closure puncture)
Intralipid 20% single dose (Fresenius Kabi; bag)	TNA should be used promptly with storage under refrigeration (2°C–8°C) not to exceed 24 h and must be completely used within 24 h after removal from refrigeration
Liposyn III 20% single dose (Hospira; glass container)	Once the outlet site has been entered, the withdrawal of container contents should be completed promptly in one continuous operation. Should this be not possible, a maximum time of 4 h from transfer set pin or implement insertion is permitted to complete fluid transfer operations (ie, discard container no later than 4 h after initial closure puncture).
Intralipid 20%, 30% after removal from the overpouch (Fresenius Kabi)	Storage for up to 72 h for unspiked and unopened Intralipid solution in the Excel container with respect to no significant peroxide formation

BUD, beyond-use date; IVFE, intravenous fat emulsion; PN, parenteral nutrition; TNA, total nutrient admixture.

Table 20. Evidence Summary, Question 12: What BUD Should Be Used for IVFE Dispensed for Separate Infusion in the Original Container and Repackaged IVFE?

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Ybarra, 2011[188]	In vitro	IVFE was repackaged in EVA containers in 50-mL and 75-mL volumes with an automated compounding device. 152 bags were compounded over 3 wk. 40 commercially prepared IVFE bags were stored under the same conditions as the repackaged IVFE. Storage times were designed to emulate hanging a bag at time 0, completion of a 12-h infusion, failing to change a 12-h infusion allowing a 24-h infusion, and refrigerated storage for 120 h (5 d) as frequently occurs with home PN. Both repackaged IVFE and commercially prepared IVFE were analyzed for contamination.	Evaluate the sterility and feasibility of using an automated compounding device for repackaging IVFE	Bacterial growth in 12 of 152 repackaged samples (7.9%) compared with none of the 40 controls. No difference in contamination rates between samples taken at scheduled times over 3 wk. 67% of all positive cultures occurred in bags after 12 and 24 h of storage at room temperature.	Did not report stratification of time to contamination 12 h vs 24 h
Crill, 2010[179]	In vitro	IVFE dispensed in 3 different dosage forms during 3 consecutive phases (original container, n = 60, repackaged into a syringe, n = 90, drawn-down of original container, n = 90) were infused for 12–14 h (12 h for repackaged IVFE, 24 h for original container and drawn-down container dosage forms). A sample from each was withdrawn from the container for culture.	Evaluate the effect of 3 different methods of IVFE dosage forms and delivery time on microbial contamination	None of the samples from original containers had microbial contamination. IVFE repackaged in syringes had a 3.3% contamination rate. There was no statistical significance in contamination rate between the 3 preparation methods.	IVFE in original containers (drawn-down and non-drawn-down) infused over 24 h demonstrated no contamination
Driscoll, 2009[194]	In vitro	Samples from 5 commercially available premixed TNA products packaged in 3-chamber plastic bags containing either 20% soybean oil emulsion or soybean oil/MCT emulsion were tested for globule size limits immediately after mixing, and at 6, 24, 30, and 48 h after mixing. Bags were stored at 24°C–26°C.	Evaluate the stability of IVFE in 3-chamber plastic bags according to globule size limits established by USP standards.	Results were dependent upon the manufacturer. Undiluted 20% emulsions from B. Braun demonstrated PFAT5 <0.05% while those of Fresenius Kabi did not.	
Driscoll, 2007[195]	In vitro	20 mL of IVFE was aseptically transferred from the manufacturer's original glass container to 18 plastic syringes or plastic bag. The study samples were attached to a syringe pump for simulated neonatal infusion over 24 h. PFAT5 levels were measured at the beginning and end of the infusion.	Investigate the differences in PFAT5 and IVFE stability of 20% IVFE aseptically transferred from the manufacturer's original packaging in conventional glass bottles or plastic bags and repackaged in plastic syringes	IVFE from original plastic containers repackaged in plastic syringes exceed USP PFAT5 limits and became less stable during simulated syringe-based infusion. IVFE from original glass containers repackaged in plastic syringes remain within the USP PFAT5 limits.	Simulated neonatal syringe study

(continued)

Table 20. (continued)

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Reiter, 2004[178]	In vitro	IVFE samples were obtained from 90 administrative sets at the end of 19- to 23-h infusions and prior to daily tubing set changes from 19 infants who received IVFE repackaged in syringes. IVFE was repackaged in unit-of-use syringes according to USP-NF standards.	Determine the effect of replacing IVFE administration sets every 24 h on contamination rate of repackaged IVFE administered to infants	Microbial contamination of IVFE infusion sets changed at 24-h intervals after infusion of repackaged IVFE was as low as 2.2%	88 samples analyzed; 2 samples from 1 patient excluded from analysis secondary to suspected bacterial migration during documented untreated *Staphylococcus aureus* conjunctivitis, bacteremia, and urosepsis. Of the 88 samples, 2 obtained from the same patient on consecutive days grew coagulase-negative *Staphylococcus*.
Reiter, 2002[177]	In vitro	2 samples taken immediately after preparation and 24 h after preparation of IVFE repackaged in thirty 5-mL syringes (test syringes) were cultured for aerobic and anaerobic growth. 30 additional samples were collected on separate occasions over 2 months from randomly chosen syringes containing residual IVFE at the end of the 20-h infusion, which was approximately 30–35 h after preparation.	Determine the sterility of 20% IVFE after transfer to plastic syringes	60 samples from test syringes and 30 samples from clinically used syringes were all negative for bacterial growth at 24 and 48 h. One test syringe grew gram-positive rods at 7 d (1.7%), and 2 clinically used syringes grew gram-positive rods at 7 d (6.6%)	
Driscoll, 1995[68]	In vitro	45 TNAs were prepared in 1.5-L volumes with the following range of components (final concentrations): AA 2.5%–7%; glucose 5%–20%; IVFE 2%–5%; monovalent cations (Na, K) 0–150 mEq/L, divalent cations (Ca, Mg) 4–20 mEq/L, trivalent cations (iron dextran) 0–10 mg/L as elemental iron; phosphate 15 mmol/L; heparin 3000 units/d, trace minerals 3 mL/d, MVI 10 mL/d. 10-mL samples were collected at 0, 6, 12, 24, and 30 h. Stability assessments included particle size analysis, pH determination, visual inspection.	Evaluate the effect of 6 independent variables on IVFE stability in TNA admixtures	Trivalent cation concentration was the only variable that affected IVFE stability	
Vasilakis, 1988[60]	In vitro	200 PN serial samples were obtained from 49 PN patients. 88 samples were obtained from patients receiving 2-in-1 + IVFE and 112 were obtained from patients receiving TNA PN. Samples were obtained after a 24-h infusion period in both groups.	Evaluate the rate of microbial growth in 3-in-1 admixtures compared with 2-in-1 admixtures with IVFE infused separately, both over 24 h	166 samples were negative (83%). Fifteen 2-in-1 cultures were positive (17%); nineteen 3-in-1 cultures were positive (17%). Contaminated samples were also stratified according to septic or clinically well patient status. There was no statistical significance between the 2 groups.	Did not take samples from the IVFE used with the 2-in-1 admixtures

(continued)

Table 20. (continued)

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Ebbert, 1987[176]	In vitro	103 consecutive 10% IVFE bottles taken from 22 patients were collected when 5–10 mL remained at the completion of infusion. 57 samples were taken from bottles infused over 5–12 h (average 10.8 h). 46 samples were taken from bottles infused 12.5–24 h (average 17.8 h). The bottles were collected with infusion set attached to simulate bedside conditions and to minimize risk of any other source of touch contamination other than attaching the infusion set to the bottle. An aliquot was removed from each bottle and cultured. Initially negative samples were cultured again after 24 h. All cultures were read at 24 and 48 h. All negative cultures were recorded as such after 48 h. Samples were also compared according to amount and type of microbial contamination.	Compare extrinsic microbial contamination rates and characteristics of contaminants from IVFE bottles infused in a clinical setting for ≤12 h with those infused for >24 h	95 bottles (92.2%) were not contaminated. 8 bottles (7.8%) were contaminated. 4 contaminated samples were taken from bottles infused ≤12 h; the remaining 4 contaminated samples were taken from bottles infused for >12 h. Sample analysis failed to demonstrate significant differences in extrinsic microbial contamination rate or organism proliferation between samples infusing for ≤12 h and those infusing 12.5–24 h.	Statistical methodology not reported
Scott, 1985[196]	In vitro Measure of PN microbial growth after intentional inoculation of compounded PN Measure of PN microbial growth of compounded PN after 24-h infusion in neonatal clinical setting	98 2-in-1 PN bags connected with a Y-connector to the IVFE container with intact infusion sets were collected from the bedside of 8 patients over 84 d. Each bag, IVFE container, and set were stored under refrigeration (mean 2.47 d, max 6 d) until sampled for culture.	Investigate the effect of IVFE addition to PN solutions on microbial growth	Contamination was detected in 8 bags (8.2%). 7 of the contaminated bags were collected from the top 2 patients with longest duration of PN therapy.	

AA, amino acid; Ca, calcium; EVA, ethylene vinyl acetate; IVFE, intravenous fat emulsion; K, potassium; MCT, medium-chain triglycerides; Mg, magnesium; MVI, multivitamin for injection; Na, sodium; NF, National Formulary; PFAT5, percentage of fat globules >5 μm diameter; PN, parenteral nutrition; TNA, total nutrient admixture; USP, United States Pharmacopeia.

The BUD for IVFE transferred from the original container to a secondary container is not clear because of differences in transfer technique, secondary container, contamination rates, and reported stability from experimental and clinical investigations.[60,68,176-179,188,194-196] In addition, the Centers for Disease Control and Prevention provides no guidance on infectious risk for BUD of IVFE transferred to a secondary container. Instead, the most recent statement recommends IV tubing replacement every 24 hours for both IVFE infused separately or when given as part of a TNA. Confounding the lack of consensus in stability and infectious risks reported by experimental and clinical investigations are the clinical and safety concerns with rapid IVFE infusions and use of commercially available IVFE in volumes that are considerably larger than the prescribed dose for neonates and pediatric patients.

Abbreviations

AA, amino acid
Al, aluminum
BSI, bloodstream infection
BUD, beyond-use date
Ca, calcium
CHO, carbohydrate
CSP, compounded sterile preparation
drawn-down container, original manufacturer container with some of the volume purged aseptically
EC_{50}, 50% of maximal effective concentration
EVA, ethylene vinyl acetate
FDA, U.S. Food and Drug Administration
high-alert medication, medication with risk of causing harm if administered in error

ISO, International Organization for Standardization
IVFE, intravenous fat emulsion
K, potassium
LCT, long-chain triglyceride
MCT, medium-chain triglyceride
Mg, magnesium
Na, sodium
OBS, observational study
OR, odds ratio
P, phosphate
PFAT5, percentage of fat globules >5 μm diameter
PN, parenteral nutrition
PPN, peripheral parenteral nutrition
PVC, polyvinyl chloride
RCT, randomized control trial
RR, risk ratio
TE, trace element
TNA, total nutrient admixture
USP, United States Pharmacopeia

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